SEP 28 1907.

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

Entered as Second-Class Matter at the Baltimore, Maryland, Postoffice.

Vol. XVIII.—No. 198.] BALTIMORE, SEPTEMBER, 1907. [Price, 25 Cents

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ON THE TEACHING OF PATHOLOGICAL PHYSIOLOGY.

II.

By W. G. MacCallum, M. D.,

Associate Professor of Pathology, Johns Hopkins University, Baltimore.

During the autumn term of the past year there was given the second part of a course on Pathological Physiology, the first part of which was carried out during the autumn of 1905 and described briefly in the August number of this journal for 1906. It is my desire to give here a short outline of the work done in this second part of the course and to endeavor to make clear the importance of teaching by experiments and demonstrations the nature of the functional disturbances which constitute the conditions met with by the practising physician and the hospital interne. It may not be amiss to repeat some of the arguments which were put forward in that previous paper with regard to the advantages of approaching the subject of disease from this point of view, for we are anxious that such teaching should spread further than it has already done in this country.

Since the time of Morgagni every student of medicine has

found in the anatomical changes in the organs the basis for his explanation of the symptoms of disease. He studies the phenomena of the disease and then, either with the tissues in his hands at autopsy or by referring to his autopsy experience of similar cases, he explains the sequence of these phenomena upon anatomical changes. This differs very little from an experiment in which he produces an anatomical change and watches the effect, except that here he must wait for the autopsy to learn precisely what Nature's experiment has been. Thus, the clinician is undoubtedly a pathological physiologist using as his subjects the human beings who are sick. Certain methods of planned experimentation he can apply to these patients to learn something of the character of the changes he is watching, far more indeed than was in the power of the doctors of old, but even yet there are limits which he must observe out of respect for the comfort of the patient and for other reasons, which make his observations in some respects necessarily indefinite and inexact. Pathological physiology in this sense, is thus the very oldest branch of medicine—for centuries while anatomy and the rest were obscure untrodden paths physicians have been watching night and day without pause the phenomena of disease and pondering upon their nature, testing as they could, with finger on the pulse or with sensitive hand on the hot brow of the patient, the progress of the changes and making surmises as to their outcome.

In modern times the post-mortem study of the anatomical changes that really had been going on has made these tests of greater value since it has become possible by the aid of such experience to interpret their results. Great strides have been made, too, in the perfection of the tests themselves, and all sorts of instruments, devised for the purpose of measuring and studying minutely the functional disturbances, now place the clinical methods of diagnosis and study almost on a level with the methods of the physiologist. Not quite, however, for the physiologist is not limited by consideration for the welfare of his subject in making his investigation and he can apply any method of study that he is ingenious enough to devise. While the clinician may take a tracing of the pulse or even of the heart-beat with a suitable instrument, the physiologist can insert canulas directly into each chamber of the heart and record its activities with as many manometers. The clinician may study the stools and theorize as to the character of the disturbance in the pancreas, while the physiologist may bring out the gland to the surface, establish a pancreatic fistula, and continuously study the chemical character and function of the pancreatic juices.

In teaching clinical medicine these gaps in first-hand knowledge are usually made up by the application of the knowledge which the physiologist has gained from normal cases to the pathological conditions which are found at autopsy or indicated by the methods of clinical diagnosis, but as a rule the student cannot make as minute and detailed study of the actually progressing disturbance of function as he must desire to make.

Hence the teaching of pathological physiology in an experimental way; it is nothing more nor less than clinical medicine with greater opportunities for studying the patients. Its aim is to reproduce experimentally the diseased conditions which one sees in the wards, to modify these diseased conditions in various ways, observing the corresponding alteration in the symptoms, and to observe directly with the eyes, the ears, with every possible instrument of precision applied directly, the intimate nature of the altered functional activity. The physiologist is supposed to study normal functional activities. This is the equally intimate study of disturbed or altered functional activity in a diseased organ.

It is a part of pathology co-ordinate with pathological anatomy and with pathological chemistry. No study of disease is complete with the study of its pathological anatomy without any notice of the alterations in the chemical nature of the tissues and fluids involved, nor is it complete without any observation of the disturbances of function which result.

For these general reasons it has seemed imperative that we should teach something of this disturbance of function, using methods as accurate as possible, and bringing the actual disordered functional process before the eyes of the student as he might watch a laboring engine with a broken cog in its wheels. This rather than leave him to reconstruct from his vaguely remembered pathological anatomy the probable explanation of the symptoms which he views from a respectful distance.

The course in pathological physiology was planned, then, with the idea of teaching in the laboratory of experimental pathology the nature of alterations of function in a way quite analogous to that in which the alterations of anatomical structure are taught in the laboratory of pathological anatomy. Facilities for this are afforded, as described in the previous paper, in the Hunterian Laboratory; and the course was arranged in such a way that each year the diseases of one group of organs might be studied, since it was thought that this would be more satisfactory than an attempt to cover superficially, each year, the disturbances of function of all the organs. Accordingly, the circulatory system formed the first subject and the results of that work were described in the paper referred to. The second division of the course which has been carried out this year was concerned with the diseases of the organs of internal secretion and an outline of this may be given here.

Some difficulties were encountered in this course owing to the fact that it is impossible to bring about symptoms very quickly by disturbing certain of these glands, and in such cases the graphic results which could be brought before the students in connection with lesions of the circulatory apparatus were not to be looked for; nevertheless it was generally possible to perform the necessary operation with the aid of a

portion of the class and to present the result at a succeeding meeting of the whole class. On the other hand, certain organs, such as the hypophysis, proved in our hands to be almost entirely inaccessible, at least as far as class demonstrations go.

The work in this instance was not, however, entirely experimental, for in the case of the organs of internal secretion the embryology, comparative anatomy, and pathological anatomy are subjects of such extreme interest that we spent some time in discussing those things, and on the other hand the class was taken into the wards of the hospital to observe such cases as illustrated the effects of disease of these glands. It is often possible in that way, of course, to show a picture of disease which could not be produced experimentally in animals within the time allotted to the course.

The adrenals, pancreas, hypophysis, cells of Leydig, thyroid, and parathyroid formed the chief subjects of discussion, but some attention was also directed to such structures as the corpora lutea, the carotid and coccygeal glands, the thymus, etc.

The adrenal was first taken up and studied with regard to its embryological development in several animals, but although the specimens from the lower animals are very instructive the series of human embryos which form Dr. Mall's collection gave us especially valuable information. The inwandering of the medullary elements into the solid mass of the cortex could be well traced and the development of the chromaffine reaction in later life easily demonstrated by fixation in the appropriate fluids.

Extirpation of the adrenals was shown to be followed by extremely grave symptoms, perhaps resembling those of Addison's disease in a greatly exaggerated form, but leading so rapidly to complete apathy and the death of the animal, that no good comparison could be made; such results appeared far less rapidly in rats, in which it is shown that there are frequently accessory adrenals. Efforts at determining whether this might be the result of the loss of an antitoxic organ were made by removing a large part of the blood and replacing it by a larger amount of salt solution, but although this diluting process seemed to resuscitate one animal, subsequent experiments which will be detailed separately threw much doubt on that conclusion. The blood removed when injected into a normal dog did produce an illness which lasted 24 hours, but from which complete recovery occurred. No blood-pressure elevating effect such as is produced by the extract of the gland could be obtained by means of the blood removed from the adrenal vein, even though a considerable quantity was thus obtained. Indeed it could hardly be expected that there should be enough blood-pressure raising material in the blood passing through the veins of an adrenal within a few minutes to produce any marked effect upon a normal dog.

The anatomical studies of the adrenals from various autopsies showed that in some cases very extensive destruction of the adrenals had occurred without Addison's disease, while it is well known that in some cases of Addison's disease the adrenals show no very apparent lesion. Interest, therefore, attaches to the minute study of the entire chromaffine system, including all the sympathetic ganglia and the carotid bodies in cases of Addison's disease in order that Wiesel's theory that the disease is dependent upon the destruction of all the chromaffine tissue may be proven or disproven.

The carotid bodies were studied anatomically and embryologically and were extirpated from a dog; no definite result followed this experiment, however, and the dog recovered entirely.

At this time a remarkable case of acromegaly appeared in the hospital, and the class was taken to the wards to study him. In connection with this the anatomical changes exhibited by a previous case which had come to autopsy were demonstrated, and the relations which the hypophysis cerebri bear to acromegaly discussed. Attempts to repeat the operation described by Friedmann and Maas for the extirpation of the hypophysis were unsuccessful and have not since been repeated, but it is proposed to carry out such experiments during the year.

The pancreas was studied only in so far as it has to do with diabetes; and the development, histology, and pathological changes in the islands of Langerhans, and in the pancreas in general, were considered in this relation. The form of diabetes produced by the extirpation of the pancreas was studied in detail. It was found that intense glycosuria appeared half an hour after the extirpation of the gland, the maximum amount of sugar being reached only after three or four hours. The sugar was present at times to the extent of 5 per cent. At no time, however, was it possible to demonstrate the presence of any of the series of acetone bodies, although in several cases they were tested for carefully.

On the chance that the control of carbohydrate metabolism might be restored by the replacement of pancreatic substance a quantity of emulsion of pancreas was injected into the peritoneal cavity after the extirpation of the pancreas had been completed for several days. No definite change in the glycosuria was thus produced however. Partial extirpation was shown to have no effect as far as the production of glycosuria goes, even when by far the greater part of the gland is removed, leaving only that portion which is attached to the intestine. Interesting material for the study of regeneration of the pancreas was furnished by these experiments. In other cases the ligature of the duct of part of the pancreas or even of the ducts near the intestine, cutting off the whole pancreas from secreting into the intestine, was not followed by diabetes. The portion of the tail of the pancreas separated by the ligature from the rest, did, however, in the well-known way, undergo an extreme atrophy, the islands of Langerhans alone remaining well preserved.

The interstitial cells of Leydig in the testicle were studied under various conditions anatomically and embryologically and experiments are still under way in the hands of one of the students, with the aim of determining the effects of ligation

of the vas deferens, of replacing the testicle in the abdomen, etc. The experiments tend to show that these cells are independent of the spermatogenic tissues and interest centers on their relation to the development and maintenance of the secondary sexual characters. Similarly, the rôle of the corpora lutea was discussed in the light of Fraenkel's work on the subject and in one case of early pregnancy in a dog a corpus luteum was excised from each ovary; no others could be seen. The dog recovered perfectly, and no further signs of the pregnancy were to be observed. Still such an experiment is by no means conclusive and only a very large series can definitely establish the relations which Fraenkel claims hold good.

In the case of the parathyroid, study of the anatomical and embryological relations were made, after which the effect of ablation of the glands was shown. Tetany develops with great regularity in dogs after the extirpation of four parathyroid glands and in this case it was characteristic. The infusion of a quantity of salt solution into the vein after bleeding abolished the symptoms of tetany completely for a period of several days. It was further shown that emulsion of the parathyroid gland injected into the veins would also cure the weli-developed tetany.

One case came to our notice in another hospital, in which the thyroid with most of the parathyroid tissue was removed from a little girl. Violent tetany developed after three days but was relieved by the subcutaneous injection of an emulsion of the parathyroids of the cow. Evidently enough parathyroid tissue remained to carry on the function; for after two such attacks had been treated in this way, the symptoms returned no more and the child has apparently recovered completely. It remains to be seen whether some special strain such as pregnancy or lactation will bring about the tetany again from parathyroid insufficiency.

Extirpation of the whole of both thyroid lobes leaving the parathyroid which was at the upper pole of each resulted in no tetany, and the dog lived in perfect health for several months, when he died of pneumonia. At the autopsy several masses of thyroid tissue had developed about the trachea, and beneath the arch of the aorta. These were very small, about the size of a pea at most, and all together would not equal in bulk one of the thyroid lobes. Histologically they show the characters described by Dr. Halsted, in compensatory hypertrophy of the gland. It is apparently impossible to produce myxœdema in such an animal as the dog, on account of the presence of these accessory thyroids, which are so small and in part so inaccessible, as to be quite invisible at the time of the extirpation of the main gland, but which then hypertrophy to meet the demand for thyroid tissue.

Experiments on the effect of extirpation of the thyroid and of the thyroid and parathyroid together in sheep and goats will be detailed separately. The anatomical conditions, as is well known, differ greatly from those in the dog, and the complete extirpation of the parathyroids usually involves the destruction of the thyroid, since one parathyroid on each side is deeply embedded in the thyroid. As a rule the symptoms following such extirpation were slight or not noticed at all, but in two goats we succeeded in producing violent tetany which agreed closely with that seen in dogs.

Cases of goitre and exophthalmic goitre were studied by the class in the wards and the clinical signs correlated with the ideas previously obtained of the functions of the thyroid. One case of exophthalmic goitre was followed by the class until the operation, after which the extirpated thyroid was studied anatomically, the usual modifications of the gland being found while the parathyroid glands removed with the thyroid showed no alteration whatever.

At the time there were not as many cases of goitre in the hospital as usual, but whatever material was available was used; in lack of this the rich material of the pathological museum was demonstrated, illustrating goitre formation, and the chemical relations of the colloid substance in normal and diseased thyroids discussed. The dependence of the growth of goitres, whether of the diffuse colloid type, the adenomatous nodular type, or the exophthalmic type, upon these chemical relationships and the corresponding needs of the body were entered into and debated. One case in which myxœdema existed as the result of almost complete disappearance of the thyroid will be detailed in a separate paper. In this case the parathyroids were unchanged and their complete independence of the thyroid thus proven.

The work in connection with these organs has been continued by some of the students of the class; and papers follow on the anatomy and topography of the parathyroids in various animals used for experimentation, on the absence of any appreciable amount of iodine in those glands, on the production of tetany in herbivora by the extirpation of the parathyroids, etc.

Next year it is proposed to continue this course, taking up the study of the functional disturbances of the organs of respiration. The work is arranged in the new schedule especially for students of the fourth year, who may now, during one trimester, elect it as their major subject of study, when they will be required to devote three hours daily for eleven weeks to the experimental study of some problem, and if possible to present a thesis on that subject. Others who choose experimental pathological physiology as a minor elective subject will attend the demonstrations which are given twice weekly. The course is, however, open to all students who have a sufficient knowledge of the normal physiology and pathological anatomy of the organs studied.

Such a summary as this is published in this way in order to show the general character of the work which we are trying to promote in the system of medical education and in the frank endeavor to enlist the enthusiasm of others who may be able to put themselves in a position to teach pathology in this way.

THE RELATION OF IODINE TO THE PARATHYROID.

By W. L. ESTES AND A. B. CECIL.

(From the Hunterian Laboratory of Experimental Medicine, Johns Hopkins University.)

Subsequent to the discovery by Baumann of iodothyrine, the active principle of the thyroid gland, the possibility of the presence of an iodine containing compound in the parathyroid was first suggested by Gley (1). He carried out his investigations on rabbits and dogs, estimating the iodine of each thyroid and parathyroid of the same side. Baumann's method for detecting iodine was slightly deviated from; for, instead of making the combustion in a crucible with sodium hydroxide, a porcelain dish with the dried glands was introduced into a Bohemian glass tube at one end of which a current of oxygen was permitted to enter and at the other end was placed a vessel with 2 to 3 cc. of sodium hydroxide. After the combustion was completed the apparatus was washed with hot water and the solution used for the determination.

Gley thus found in the rabbit's parathyroid, absolutely 2.35 times as much iodine as in the thyroid and relatively 37 times as much; and in the dog the parathyroid contained absolutely less (about one-fifth) than the thyroid, but relatively it contained 16 times as much.

Gley, therefore, concludes that the parathyroid must play some part in the "Thyroid System of Organs," the parathyroids preparing the product of secretion which is then transferred in some way to the thyroid and finally utilized according to the demands of the organism (2).

Lafayette Mendel is widely misquoted as having found great quantities of iodine in the parathyroid. The paper to which reference is made, "On the Occurrence of Iodine in the Thymus and Thyroid Glands" (3), discusses the presence of iodine in accessory thyroids and the thymus, and not in the parathyroids, and in this connection Mendel refers to the presence of iodine in the spleen, adrenal, salivary glands, and makes casual mention of Gley's finding iodine in the parathyroid. It is his concluding statement that has probably been misconstrued: "Accessory thyroids in man may contain both relatively and absolutely more iodine than the thyroid proper of the same individual."

Jeandelize in discussing the chemistry of the parathyroid in his monograph (4) reaches a conclusion similar to that of Gley, believing not only in the "Thyroid System of Organs," but adding "That this hypothesis agrees very well with the physiological effects of extirpating the gland"; *i. e.*, he believes that the iodine is disseminated in the organism after having been stored in the thyroid and previously prepared for assimilation in the parathyroid. In case of parathyroidectomy the iodine is not properly prepared and the organism suffers acute intoxication. On the other hand, after thyroidectomy the storehouse and distributor of iodine no longer exists, no acute symptoms arise since the iodine has been purified in the parathyroid, but malnutrition is in evidence because the iodine is not distributed according to the demands of the organism.

Chenu and Morel (5) more recently have worked on chickens, dogs, and rabbits. They used in their determination equal weights of thyroid and parathyroid tissue and followed Baumann's method: potassium hydroxide for combustion and carbon disulphide for the color test. They were thus able to read to .0025 mgr. of iodine. In no case in which they examined the parathyroid of a single animal could they detect any iodine, although the same amount of thyroid from that animal was found to contain a quantity of iodine which could be estimated. When they combined the parathyroids of eight dogs they were able to demonstrate iodine (.0563 mgr. to 1 grm. of fresh parathyroid). They conclude therefore that the thyroid and parathyroid differ chemically and that the active principle of the parathyroid is not an iodine-containing compound.

At the suggestion of Dr. Wm. G. MacCallum we have repeated this investigation on the parathyroid of dogs, cows, horses, sheep, and man. Instead of taking a single parathyroid for a determination as hitherto, we have used many parathyroids, drying them as collected on glass plates at room temperature.

For analysis we have used Baumann's method as stated by Kocher, preferring to use chloroform rather than carbon disulphide for the colorimetric test. The dried glands were weighed and placed in an iodine free crucible with 5 cc. of water and 2 gr. of sodium hydroxide for every gram of the glands. This mixture was evaporated to dryness over a flame and ashed. Then an amount of potassium nitrate equal in weight to the amount of sodium hydroxide used was added, and the mass heated till it assumed a white appearance. The crucible was then cooled and treated with 20 cc. of water, then heated and the liquid filtered; the crucible and filter paper being thoroughly washed with hot water. The cooled filtrate was treated with 20 per cent sulphuric acid and shaken well with 5 cc. of chloroform. If iodine is present the chloroform assumes a pink tint.

Iodine may be determined quantitatively by a comparison of this color with that produced by a known quantity of a standard potassium iodide solution thoroughly shaken with 20 to 25 cc. of concentrated sodium sulphate, 10 to 12 drops of a 1 per cent solution of sodium nitrite, 3 to 5 cc. of sulphuric acid (20 per cent) and 5 cc. of chloroform. By careful manipulation the color produced in the chloroform by the unknown can be matched by the color produced by the known amount of potassium iodide; and thus the amount of iodine present is computed. Iodine to the amount of .0025 mg. could be detected.

The crucible used for each determination was tested for

iodine by running through the above process and noting whether a color with chloroform was produced or not, thus rendering it iodine free. Gentle heat was invariably found to produce the quickest and best results, easier filtering and clearer filtrate; iodine is also volatile under great heat.

The following are our results:

ANIMAL.	WT. OF DRIED GLANDS.	AMT. OF IODINE.
Dog	.25 grams.	Infinitesimal.
"	.24 "	"
Cow	5.00 "	Negative.
"	5.00 "	"
"	1.00 "	"
"	1.00 "	"
"	1.00 "	"
"	1.00 "	"
Horse	3.78 "	.06 mg.
"	.743 "	Negative.
"	1.135 "	"
Sheep	.2276 "	"
"	.225 "	"
Man	.87 "	"
"	.61 "	"
"	.3316 "	"
"	.26 "	"

It will be seen that though large quantities of parathyroids were used for each determination in but three instances was the slightest trace of iodine detected and this in such trifling amounts as to be insignificant in importance. To confirm our work from time to time control experiments were made by adding a small amount of potassium iodide to the dried glands. This mixture was then put through the process, and in every case the amount of iodine added could be computed by the colorimetric method.

It should be noted that especially in such an animal as the dog it is difficult to dissect out the parathyroid in such a way as to be certain that no thyroid tissue is included in the mass removed. In many cases this is true also of the human parathyroid and it seems probable that in those instances in which iodine was detected in the parathyroid material it may have been due to the accidental admixture with thyroid tissue.

These results are not markedly different from those of Chenu and Morel, who in reality found extremely minute quantities of iodine in the parathyroid, and though Gley's experiments stand so emphatically contrary to what we have found, yet in view of the wide field our experiments embrace we conclude:

(1) That iodine as a constituent of the parathyroid may, generally speaking, be neglected.

(2) That if present at all iodine occurs in such minute quantities as to be of no functional significance.

(3) We fail to find chemical grounds for the hypothesis of the thyroid system of organs.

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PANCREATIC ATROPHY IN A DOG FOLLOWING IMPACTION OF CALCULI IN THE DUCT.

By R. D. McCLURE,

(From the Hunterian Laboratory, Johns Hopkins Medical School.)

An interesting condition of the pancreas, produced by concretions in the duct of Wirsung was discovered in an autopsy on a dog in the Hunterian Laboratory. It is reported at the suggestion of Dr. MacCallum.

The pancreas was lying free from the surrounding tissues and was nowhere bound by adhesions. The tail presented a striking appearance. It was dark colored, curiously nodular and shrunken, and much smaller and firmer than the remaining portion of the pancreas. The total length was 15 cm. The shrunken tail measured only 2½ cm. and passed abruptly over into normal looking pancreas On section the parenchyma of the head end was normal in consistency and appearance. The characteristic lobulation in the small amount of tissue of the shrunken end was entirely absent, being replaced by connective tissue in which minute bulgings could be made out.

The longer proximal portion of the duct was found to be normal and contained a grayish opalescent fluid. A probe passed through the papilla met no resistence and the lumen was patent as far as the shrunken portion where it suddenly became constricted, causing complete occlusion. The duct distal to the occlusion was greatly dilated and formed by far the greater portion of the shrunken mass. This cavity was distended by a thick grayish fluid. The search for the exciting cause of the constriction revealed two minute calculi, tightly impacted in the constricted lumen. These were small, round, slightly rough, opaque bodies, not larger than the head of a pin. Careful examination failed to reveal any more such

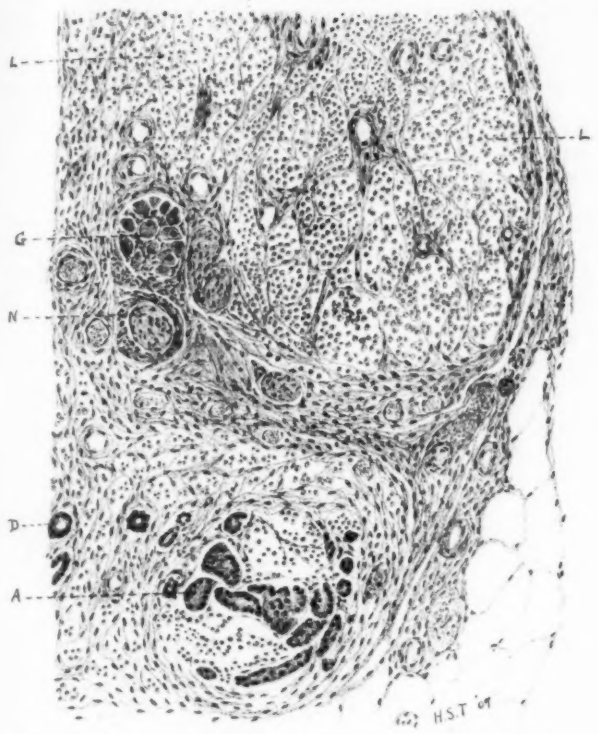


FIG. 1.—Portion of atrophied pancreas distal to obstruction of duct. *L*, degenerated parenchyma; *G*, ganglion with large nerve cells; *N*, nerve trunk; *D*, small branch of pancreatic duct; *A*, remnants of island of Langerhans.

bodies, either in the lumen of the duct or in the surrounding tissue.

With the kind assistance of Dr. Loevenhardt these concretions were analyzed and were found to be composed of calcium carbonate with only a trace of proteid.

The microscopical picture was an interesting one (Fig. 1). The parenchyma, islands, and ducts of the proximal end were normal in every particular. Distal to the constriction, at first glance the tissue would not be recognized as pancreas. The duct epithelium was degenerated and in many places desquamated. The surrounding tissue was largely composed of connective tissue in which were embedded large numbers of cells of the islands of Langerhans. These, however, did not appear normal and were no longer in columns as in the normal island, but were very irregularly arranged and widely separated, by connective tissue which invaded these areas.

Only a few remnants of the normal acini were present. These were far apart and entirely surrounded by connective tissue. The cells were degenerated and did not stain clearly.

The blood vessels were well filled with blood and many non-medullated nerves were seen in the section. In the accompanying drawing by Mr. Herbert S. Thomson a large ganglion is seen.

The small portion of pancreas affected was probably not great enough to alter in any way the metabolism of the dog, even if the Islands of Langerhans, too, had been entirely destroyed.

TETANY AFTER PARATHYROIDECTOMY IN HERBIVORA.

By W. G. MACCALLUM, M. D., H. S. THOMSON, AND JAMES B. MURPHY.

(From the Hunterian Laboratory, Johns Hopkins Medical School.)

The statement has been so generally made that no evil results follow the extirpation of the thyroid and parathyroids in herbivorous animals that it has seemed to us very remarkable at least, and worthy of investigation. The less toxic character of the decomposition products of the food of herbivora is usually assigned as the reason for this absence of tetany and the idea was even put forward in another way by Verstraeten and van der Linden who stated that after parathyroidectomy in dogs they could prevent the appearance of tetany if they fed the dogs on milk only. This is, however, not true as was shown by some of our experiments recorded in a previous paper.

We had the idea in approaching this investigation that previous workers had possibly overlooked some parathyroid tissue so that after the operation there still remained enough to prevent tetany. Indeed as will be seen from our results this idea is still in our minds after our own experience with sheep and goats. We did, it is true, find four parathyroids in every case very regularly situated in the thymus and thyroid, and the most painstaking and minute dissection of the remaining tissues at autopsy never revealed any further trace of parathyroid tissue, but still the suspicion remains that somewhere there is more of that tissue. In sheep and goats the distribution of the parathyroids is quite the same. There are two embedded or partly embedded in the thymus, one on each side at the level of the thyroid cartilage of the larynx and just in front of the carotid and vagus nerve. As is well known the thymus in these animals extends from the submaxillary gland down into the thorax, although it is not always quite continuous throughout this distance, and the parathyroid is quite easily distinguished as it lies in this pale cream colored tissue. After a little pulling aside of the lobes of the thymus it springs into view as a bright red rounded smooth body about 3-5 mm. in diameter. Its homogeneous appearance and red color render it easily distinguishable from the lymph nodes which are sometimes found scattered in the same tissue. It is quite sharply outlined and distinct from the thymus, but is apparently supplied with blood by a branch of one of the vessels supplying the thymus.

The thyroid consists of a rather small lobe on each side

united across the front of the trachea by a delicate band or isthmus. Embedded in each of these lobes is the remaining parathyroid. These masses which we have found in the thyroid in every case cannot be clearly seen in the living animals, and we have found it necessary in order to secure their extirpation to remove the whole thyroid lobe each time. In hardened tissue, however, they stand out fairly plainly on section from the surrounding thyroid tissue. They are not furnished with any capsule, but come into very intimate relation with the thyroid tissue. No very definite statement can be made as to their exact position in the thyroid because this seems to vary a good deal.

As noted above most diligent search has been made through the rest of the tissue of the head, neck, and thorax for any further parathyroid tissue, but without avail, although quite a number of animals have been thus carefully dissected.

Histologically the parathyroids of sheep and goats are practically not to be distinguished from one another. The tissue of that gland which is embedded in the thymus is quite identical with that of the intrathyroid gland, and on this ground it seems to us that the so-called parathymus gland of Schaper and others is undoubtedly merely the second parathyroid.

The glands are very compact and very vascular. The cells are apparently all of one type and are closely arranged in anastomosing strands and cords so that the intervening capillaries come into direct contact with all the cells. The cell nuclei are large and round and the cytoplasm very abundant with a somewhat granular structure. The perfectly clear cells and the eosinophile cells seen in the human parathyroid are not to be found here. Nor are they evident in the parathyroids of various other animals such as the dog, the horse, cow, cat, etc.; occasional cells suggesting the eosinophile type may be seen but in such definite grouping as occurs in the human parathyroid they are not to be found. The structure of the goats parathyroid is shown in the accompanying figure.

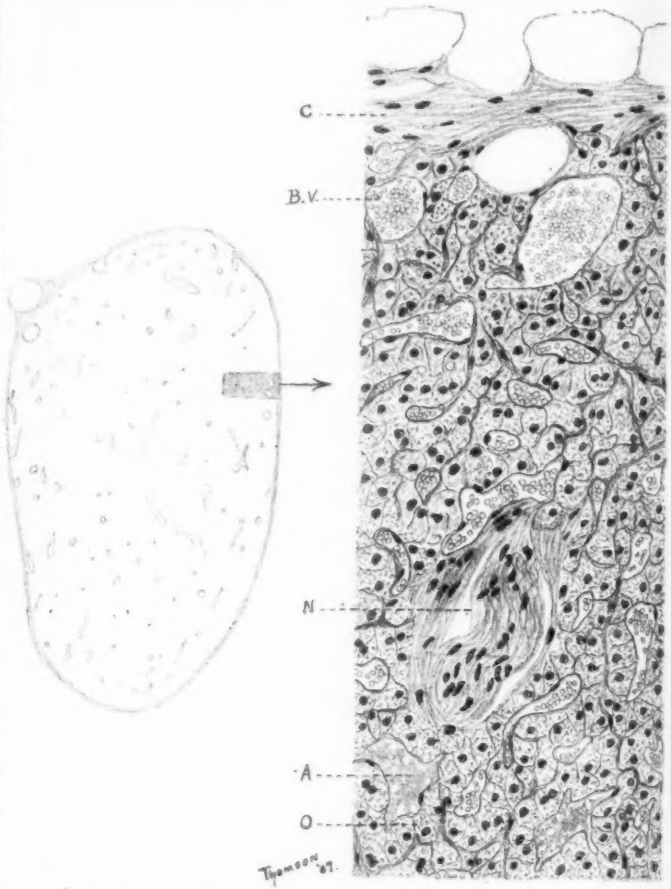
The experiments which we undertook for the purpose of controlling the current statement about tetany in herbivora were carried out on eight goats and five sheep. The two parathyroids embedded in the thymus were removed, sometimes together with part of the thymus and the two thyroid lobes were removed at the same time. Wound healing was perfect in every case.

The histories of these cases are briefly as follows:

Goat A.—Operation on Dec. 13. On Dec. 15 distinct and quite intense twitching was observed in fore and hind legs. At certain moments this was so intense that the goat had not the use of his hind legs which were stretched out stiffly behind. Respiration was not affected and later in the day the twitching practically disappeared. On Dec. 17, the animal was unable to stand, respiration labored, but no tetany. This condition continued until Dec. 19, when he was found dead. At the autopsy no parathyroid tissue was found and no changes in the organs were discoverable which could account for death.

Goat B.—Old goat. Operation June 8, 1907. Thyroid removed with two bodies which subsequently proved to be lymphglands. No symptoms up to Jan. 11, when a second operation was performed, and the two parathyroids removed from the thymus. No symptoms until Jan. 21, when there was definite twitching in the legs and body wall. This disappeared next day and remained absent. There were no symptoms throughout February, but on March 9, the animal was found dead. At the autopsy nothing was found to account for death, and no further parathyroid tissue could be discovered.

Goat C.—Small kid. Operation March 29. Four parathyroids together with thyroid and thymus removed. Animal died of pneumonia March 31, having shown only indefinite quiverings.



Parathyroid of goat. *C*, capsule; *Bv*, blood vessel; *N*, nerve; *A*, alveolus with granular content; *O*, epithelial cells.

Goat D.—Small kid. Operation May 4, 1907. Two parathyroids and both thyroid lobes removed. Accidentally killed May 13, without having shown any symptoms. At autopsy no trace of thyroid or parathyroid tissue.

Goat E.—Small kid. Operation May 5, 1907. Parathyroids, thymus, and thyroid extirpated. No symptoms until May 16, when the animal was found in violent tetany, lying on the floor in convulsions with rapid labored breathing. This passed off later, but distinct twitchings could be felt in the muscles, especially about the head and ears. Next day the same violent tetany reappeared, and the goat died in this attack. At autopsy no trace of parathyroid tissue could be found, nor any lesions in the other organs which could account for death.

Goat F.—Angora kid. Operation May 22. Parathyroids, thymus, and thyroid removed. In this goat which is still alive (July 7) slight twitchings have been observed from time to time, but there has never been any violent tetany. Given several large doses of Liebig's extract without any effect.

Goat G.—Angora kid. Operation May 23. Two parathyroids, thymus, and thyroid removed. Some twitching observed during next three days. Given large doses of Liebig's extract without any effect. May 31, at 6 p. m., the goat was found in violent tetany, legs very stiff, breathing deep and slow, head constantly thrown far back. Next morning it was again found in violent tetanic convulsions, unable to stand, twitchings exactly as in dogs without such great rigidity; fibrillary tremor of tongue well marked. The animal was given subcutaneous injections of ox parathyroid, but the tetany continued together with the opisthotonic drawing back of the head. Later in the evening the weakness and opisthotonos were alone evident, the twitching had stopped. June 2, 10 a. m., again in marked tetany with much rigidity of legs. Found dead at 3 p. m. At autopsy there was found a quite extensive lobular pneumonia.

Goat H.—White kid. Operation May 26. Parathyroids and thyroid lobes from each side extirpated. This animal is still alive July 7, and has shown no symptoms whatever.

The results obtained by operating on sheep were as follows:

Sheep A.—Operation Jan. 8. Two parathyroids and thyroid removed. Only most indefinite twitching observed during next few days. Death occurred Jan. 15 from pneumonia.

Sheep B.—Operation Jan. 8. Two parathyroids and thyroid extirpated. No symptoms up to Feb. 19, when another operation was performed and all the thymus removed from the neck. Death during night.

Sheep C.—Operation March 12. Two parathyroids and thyroid removed. Examination of the thyroid revealed as usual two parathyroids. No symptoms at any time.

Sheep D.—Operation Mar. 14. Two parathyroids, thyroid with two parathyroids and part of thymus removed. No symptoms except slight twitching on Mar. 20. Death from pneumonia Mar. 22.

Sheep E.—Operation Feb. 20, 1907. Parathyroids and thyroid removed. No symptoms up to Mar. 19, when another attempt was made to remove what was left of the thymus in the hope of extirpating any possible accessory parathyroids. No symptoms followed this. Sheep died April 12, much emaciated. No pneumonia.

From these experiments it is seen that there is indeed a very marked difference between the results obtained by parathyroidectomy in the dog and those in such animals as the sheep and goat. Practically no effect whatever was produced in these five sheep, although in at least three of them ample time elapsed for the development of symptoms. It is true that there was observed from time to time a slight twitching, but this was so indefinite that it cannot be regarded as typical tetany. In sheep B, C, and E a marked emaciation followed with some apathy which resembled that occasionally produced in dogs after such an operation but on the whole the results must be regarded as practically negative. All of these sheep were mature animals and as will be seen from the experiments on the goats the most definite results were there obtained in very young ones; possibly further experiments with lambs might show that it is possible to produce tetany in them.

In the case of the goats there was fairly definite twitching without actual tetanic convulsions in four; two showed no symptoms at any time, while two developed perfectly typical and extremely violent tetany leading at least in one case to the death of the animal. The feeding of proteid and extractive material such as Liebig's extract seemed to have no influence whatever upon the outcome of the experiment. From these two positive results, however, it is clear that the extirpation of the parathyroids is not such a completely indifferent proceeding as has generally been stated.

We do not know how to explain satisfactorily the negative results in so many of these animals unless it be that in spite of our extremely careful and conscientious search there are still other masses of parathyroid tissue hidden away somewhere in the neck or thorax. It does not seem reasonable to suppose that organs which are so clearly shown to have a special function in carnivorous and most other animals should be so highly developed in the herbivora and still have no special functional importance.

We may conclude that for some reason, possibly a wide distribution of parathyroid tissue, it is difficult to produce tetany in herbivora by removing the main masses of that tissue but that it is shown to be possible at times by the two cases in which typical violent tetany was produced in the goat.

THE PARATHYROIDS OF THE HORSE.

By WM. L. ESTES, JR.

(From the Pathological Laboratory, Johns Hopkins University.)

The parathyroid gland was discovered in the horse by Sandström, in 1880, who described but one gland situated at the superior extremity of the thyroid body. Moussu repeated Sandström's observations and found the gland situated in the peri-thyroid tissue along the thyroid branch of the thyro-laryngeal artery which comes off the common carotid artery just at the lower pole of the thyroid and passes toward the larynx, supplying the thyroid by a branch given off at its superior pole. Verdun, on the contrary, finds the parathyroid separated from the thyroid only by its capsule; while Blanc asserts he was never able to find one. Jeandelize, in reviewing the subject from the above observations, concludes there must be a variability in position of the parathyroids in this animal. He further believes in the light of comparative anatomy and of experimental evidence that there is another parathyroid constantly present, either embedded in the thyroid itself or situated somewhere in the peri-thyroid tissue. Comparative anatomy teaches that in all other animals there are four parathyroids, two on each side. The only experimental study is that of Moussu, who removed from a horse first the parathyroids and then the thyroids without producing tetany. Therefore Jeandelize leans to the view that the "unknown"

parathyroid lies somewhere in the peri-thyroid tissue; i. e., the horse has four parathyroids, all external and outside the thyroid gland. More recently Rogers and Ferguson mention in a paper on the anatomy of the parathyroid that they find in the horse, usually along the posterior border of the thyroid, an external parathyroid, which they detect with some difficulty from neighboring thyroid and lymphatic glands; and *an internal gland* situated within and near the middle of the thyroid.

Our study was concerned with the anatomy and topography of these parathyroids of the horse. The external gland was found without difficulty; it varies from the size of a marrow fat pea to that of a hazel nut; it is usually pale yellow-gray, occasionally salmon-pink and on congestion assumes a deep purple-red color. Its consistency is soft but not flabby. It has a peculiar lobulated appearance normally, which is not more prominent with congestion. On cut section the perfectly typical coarsely granular appearance is invariably present and distinct lobules can be easily made out with often a central vessel; this permits of ready differentiation between thyroid, lymph gland, and parathyroid; neither of the former resembling on cross section this characteristic picture.

This gland occurs in a somewhat variable position. Out of 125 glands examined: (1) 42 were found closely adherent to the superior pole of the thyroid. (2) 54 were found in the peri-thyroid areolar tissue, always associated with the thyroid branch of the thyro-laryngeal artery. This breaks up close to the superior pole of the thyroid into numerous ramifications which pierce the thyroid directly or follow its lateral border inferiorly and eventually enter its substance. In this mass of vessels the parathyroids of this class are found and therefore they lie near the superior pole of the thyroid. (3) 28 were found adherent to the lateral margin of the thyroid near its middle; in this case the branching of the thyroid artery was unusually low. (4) 1 parathyroid was found at the inferior extremity of the thyroid, loosely adherent. Thus this parathyroid may be considered to be associated with the branching of the thyroid artery, its position varying with the variations of the artery but in the great majority of instances it is situated on or near the superior pole of the thyroid.

Microscopically, the gland is seen to be surrounded by a thin capsule which sends in fibrous strands as a supporting framework carrying blood vessels. The afferent vessels enter the centre of the gland and branch outward to the boundaries. The capillary net-work is extraordinarily rich, the wide capillaries being separated nowhere by more than two cells. It is of interest to note that Evans has found in the human parathyroid a similar central afferent vessel.

The gland tissue occurs in masses and strands irregularly anastomosing and rarely showing anything resembling an alveolar lumen. These masses are made up of anastomosing cords of cells separated as mentioned by very wide capillaries. The cells vary in appearance assuming forms almost like those seen in the human parathyroid. Three varieties may be distinguished fairly well. Of these the first has a spherical or ovoid nucleus, containing many dark staining chromatin granules and a cytoplasm which is quite clear and takes no stain. The second kind, which is the predominant type of cell, has a similar nucleus but its protoplasm is stained a dull lilac faintly granular like ground glass. These are evidently the analogues of the faintly granular cell of the human parathyroid. The third type occurs but rarely in the specimens we have studied and is by no means so distinct as the other types. These cells are found singly, and but for their similarity to certain typical cells in the human gland; they might be regarded as degenerated cells. They have a dense homogeneous deeply stained spherical nucleus of rather small size, surrounded by a large protoplasmic body which is swollen to almost twice the size of the adjacent cells. In the cytoplasm are fine granules which take a pink stain and give the whole cell a dull red appearance.

Of the 125 glands studied 18 or about 15 per cent were found to have cystic structures adherent or continuous with them similar to those often seen bulging from the parathyroid of the cow. They are usually lobulated as if several cysts were attached at a common origin, rarely they form simple swellings on the surface of the gland. No cysts were found in the parathyroid substance. They contain a pink viscous gelatinous mass, at times quite liquid in consistency and easily evacuated when the cyst wall is cut. Microscopically it is seen that the capsule of the parathyroid runs over the cyst and forms its capsule also. In this capsule one sometimes finds masses of what is apparently thymus tissue, raising the question as to whether the cyst may possibly have originated from the thymus rather than the parathyroid. The lining is of flat squamous epithelium sometimes heaped up in several layers. Much of this is desquamated and appears in the form of large round phagocytic cells floating in the fluid content.

To determine the existence of an internal parathyroid the thyroid was hardened and cut into fine slices with a sharp knife, each slice being examined with a dissecting microscope, and suspicious areas further studied by making frozen sections. Small adenomata are extremely frequent in the horse's thyroid, however, and are confusing; even in well stained sections it is often difficult to be sure that one is dealing with an adenoma and not with a bit of parathyroid tissue, nevertheless the distinction can be surely made. In other cases the thyroids were embedded in celloidin and sectioned serially, every tenth section being examined and stained if necessary. Twenty-five glands were thus examined and the parathyroid found in thirteen of them. They seem to be distributed irregularly in the thyroid tissue, occurring often near the superior pole in a rather superficial position, but are sometimes more deeply embedded. Occasionally they are found near the lower pole. The internal parathyroid is pale in color as a rule and may thus be easily confused in gross with any small adenomatous growth though it stands out very sharply from the brown thyroid tissue. In one interesting case two internal parathyroids were found in the same thyroid. They were both darker than the thyroid, and were of comparatively large size; one situated 6 mm. from the superior pole and near

the middle of the gland adjacent to a large artery and the other just beneath the capsule where another large artery pierced it. They were both about 5 mm. in breadth by 4 mm. in length. Their color was found to be due to the overdistension of their capillaries with red blood cells.

The internal parathyroid has the lobular and alveolar structure of the external parathyroid; it is usually separated from the surrounding thyroid tissue by a thin strand of connective tissue but occasionally it shades off so gradually into thyroid that it is hard to tell just where one ends and the other begins; it is exceedingly vascular and invariably adjacent to a blood vessel.

We therefore conclude:

1. The horse has four parathyroids, two on each side.

2. One parathyroid is found at the superior pole of the thyroid in relation to the branching of the thyroid artery.

3. The other parathyroid is found variously placed beneath the capsule of the thyroid, usually near its upper pole.

4. The external gland is much the larger.

5. Further experimental evidence is necessary to prove that parathyroidectomy results in no evil consequences in the horse.

6. The horse resembles the other herbivora in the distribution of its parathyroids.

ON THE PATHOLOGICAL ANATOMY OF LYMPHO-SARCOMA AND ITS STATUS WITH RELATION TO HODGKIN'S DISEASE.

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The confusion which still exists concerning the relationship of various diseased conditions of the hæmopoietic organs to one another, depends, it seems, entirely upon our complete ignorance of their ætiology, for as seen in the case of scrofulous lymph glands, there is no difficulty in defining their status as soon as their cause is known.

No attempt can be made here to discuss all these different conditions, but the material of the Johns Hopkins Hospital has been so rich in two of them, Hodgkin's disease and lympho-sarcoma, that it seems desirable to compare those two especially, since even the anatomical distinctions do not seem clear in all minds as yet, and they are constantly confused.

Such classification as we possess is based entirely upon the morphology and mode of growth and distribution of these lesions, in other words they are distinguished much as a systematic botanist distinguishes and classifies plants. It may perhaps be advantageous to quote Sternberg's attempt at their classification, although since he is one of those who regard Hodgkin's disease as a form of tuberculosis that condition is not included in the classification, but would rationally form number 9 parallel with lympho-sarcoma.

A. Primary diseases of the lymphatic and hæmatopoietic apparatus. Local limited homologous (hyperplastic) tissue growth; (a) With discharge of the cellular elements into the blood and homologous change of the tissue of the lymphatic and hæmopoietic apparatus. (1) Lymphatic apparatus—Lymphocytes in blood. *Lymphatic leukæmia.* (2) Myeloid tissue—myelocytes in blood. *Mixed cell leukæmia.* (b) With slight or no discharge of cellular elements in the blood. (3) Of all lymphatic tissue in diffuse way. *Pseudo-leukæmia.* (4) Of the lymphatic tissue of bone-marrow in form of a tumor. *Lymphatic myeloma.* (5) Of myeloid tissue of bone-marrow in form of a tumor. *Myeloid myeloma.*

B. Atypical growths invading the neighborhood with heterotopic new growths: (a) With discharge of cellular elements in the blood. (6) Of the lymphatic tissue (discharge of ungranulated pathological cells). *Leukosarcomatosis* or *chloro-leukosarcomatosis.* (7) Of myeloid tissue (discharge of granular pathological cells). *Chloro-myelosarkomatosis.* (b) Without discharge of cellular elements into the blood. (8) Of the lymphatic tissue. *Lympho-sarcomatosis.*

The papers of Paltauf and Sternberg in Lubarsch and Ostertag's Ergebnisse, Vols. III_1 and IX_2 form the best summaries of the ideas on these subjects. As to the nature of Hodgkin's disease so much precise description has been written recently that it seems unnecessary to repeat it.[1] Dr. Reed's studies hold good in every detail as far as the histological description and general characters of the growth are concerned, and on studying five additional cases at autopsy we are not inclined to deviate from her ideas that the condition is entirely independent of tuberculosis, and that the new tissue produced has a constant histological character which is easy to distinguish from that seen in any other condition. Briefly described this new tissue consists of a reticulum and connective tissue stroma which becomes denser and more conspicuous with the age of the lesion and in the meshes of which lie at least three types of cells, first the lymphoid cells, sometimes rather elongated, second the large irregular cell with large vesicular nucleus or nuclei, with sharply stained nucleolus and third the eosinophile cells, which last are however inconstant. The picture so constituted is very peculiar and characteristic and may be recognized at any stage although this is more difficult in the late stages when the cells have disappeared in part and the stroma has become very conspic-

[1] Reed, Dorothy M. Johns Hopkins Hospital Reports, Vol. X, p. 133.

Longcope, W. T. Bull. Ayer Clin. Lab. Penn. Hosp., Phila., 1903.

Benda, C. Verhandl. d. deutsch. pathol. Gesellsch. 7 Tagung, 1904.

Sternberg. Ztsch. f. Heilk, 19, 1898.

uous. It was pointed out by Dr. Reed that this new tissue replaces the lymph glands which lose all trace of their original architecture and that nodules of identical tissue may be found in the liver or spleen. She thought that the capsule of the glands was usually respected by the growth so that the glands did not become matted together; nevertheless in the spleen and liver the growth is no respecter of surrounding tissue and since her paper, others have described the invasion and penetration of the capsules of the lymph glands.

The cases which have come under our observation since Dr. Reed's work and which were not described by her were five in number: of these the first three were cases in which involvement of the cervical, axillary, inguinal, retroperitoneal, and other glands were associated with the growth of nodules in the liver and spleen. These exhibited precisely the characters so generally recognized and we had no hesitation in making the diagnosis. The other two cases were however interesting in that in addition to the enlargement of the superficial glands there was extensive invasion of the lungs.

One of these cases was that of a woman aged 32 from whom the enlarged cervical glands were repeatedly extirpated—the examination of these rendered the diagnosis certain. At the autopsy there were found enormously enlarged bronchial glands, with masses of the new tissue extending into each lung and numerous smaller isolated nodules scattered through the lung substance

There were no other organs involved. The sections showed in the pulmonary nodules the characteristic tissue, which had here behaved much as a malignant tumor might behave, filling up some alveoli and compressing others. The trachea was pierced by the tumor growth also and nodules projected into its interior.

The other of the two cases was that of a boy aged 15, in whom there was general enlargement of the lymph glands and flatness over one lung. At autopsy the affected lung was found to be solid and covered by a thick white œdematous pleura. The cut surface showed that most of the lung tissue was replaced by grayish translucent nodules, measuring 1 to 4 mm. in diameter, separated by the opaque yellowish pink compressed lung substance. Microscopically both the glands and the nodules in the lung were found to be composed of a tissue which although very fibrous, could be definitely recognized as the characteristic tissue of Hodgkin's disease.

From several of these cases portions of the tissue have been implanted in the subcutaneous tissues of rabbits, but never has any tuberculosis resulted. Tissue from a recent case from which a gland was extirpated at operation was stained by Levaditi's method and searched minutely for spirochaetæ, but with negative results.

In sharp contrast with these cases, stand eight cases of lympho-sarcoma. As to the definition of the group of lympho-sarcomata or the condition lympho-sarcomatosis we are helped very little by the writers previous to Kundrat, although the condition was seen and recognized as different from leukæmias and forms of sarcoma.

Kundrat describes as lympho-sarcomatosis a more or less widespread lesion with tumor formation arising from a lymph gland, or a group of them or from some lymphoid tissue such as occurs in the intestinal wall, pharynx, etc. Such a tumor mass is composed of a delicate reticulum in the meshes of which lie cells rather larger than lymphoid cells. It fails to respect the capsules of the lymph glands, but grows rapidly and invades and infiltrates the adjacent tissues.

It is thought that the growth may occur by transportation of the cells by way of the lymph stream, as well as by direct extension and implantation, but in these cases too, the continuity of the growth can be fairly well established by discovering the involvement of the intervening lymphatic glands, etc. The tumor tends to spread in loose tissue and in film or plate form over serous surfaces. Metastases in distant organs explainable only by transportation by the blood stream are uncommon.

The tumor forms large infiltrating masses in the mediastinum or in the cervical or pharyngeal region, or in other cases involves the intestinal wall where it may cause a diffuse thickening of the wall with a widening of the intestine at the involved area. In such cases it is not uncommon to find other organs such as the adrenal and pancreas practically buried in an infiltrating mass of such tissue. Where the tumor appears in nodular form in such organs as the heart, kidney, etc., the sharply outlined nodule seen with the naked eye proves to be only a fairly localized infiltration, the muscle fibers or tubules being merely separated by infiltrating cells.

Our eight cases fall perhaps by chance into two fairly distinct groups, in one of which the main lesion consists in a great mediastinal tumor mass with involvement of the thoracic organs without affecting the abdominal organs. In the other group the most striking lesions were in the intestinal wall with other tumor masses involving the other abdominal organs, such as the liver, stomach, pancreas, adrenal, kidneys, etc. These are composed of cells rather larger than those found in the thoracic growths, and contain many large phagocytic cells. It seems probable from this distribution that if it be true that some unknown infectious agent causes this growth, the infection may begin in the one group in the tonsils, pharynx, etc., while in the other cases it invades through the intestinal mucosa.

The cases are as follows:

Case 1.—Autopsy 22, was that of a man aged 27, in whom there was found in addition to great enlargement of the cervical glands, which were matted together, a great mass surrounding the base of the heart and extending downward into the anterior and posterior mediastinum, compressing the lungs. Microscopically the new tissue was found to consist of a delicate stroma containing small lymphoid cells 5-8 in diameter.

Case 2.—Autopsy 1402, that of a colored woman aged 60, in whom at autopsy there was a mass 6 x 8 cms. which lay in front of the root of the aorta, with a similar mass behind; all the pericardial lymph glands were enlarged and the pericardial cavity obliterated by adhesions, and on opening the heart it was found that the tumor mass had grown down over the surface of the heart and had penetrated its muscle so as to partly replace the wall of the right ventricle and to hang in polypoid masses into its lumen. The other organs were not involved.

Microscopically the new tissue is uniform everywhere, and composed of cells measuring 5-12 μ supported by the most inconspicuous reticulum. The cells in this case are sometimes rather elongated and coherent, so as to form a denser tissue than usual.

CASE 3.—Autopsy 2111, was that of a boy 7 years of age, in whom all the lymph glands were enlarged and there was found at autopsy a great mass filling the thorax and embedding the heart and compressing the lungs. There was some invasion of the pectoral muscles and of the pleural and pericardial tissues, but no involvement of the abdominal organs. The cut surface of the tumor appeared as a gray, soft, moist, but fairly coherent tissue, which on section was seen to consist of a very sparse and extremely delicate reticulum, in which lay rounded cells measuring from 4-7 . The bone-marrow is composed of a solid mass of cells resembling those of the tumor and so too are the enlarged lymph glands. The capillaries of the liver are filled with the same cells, and enquiry reveals the fact that during life the blood showed 230,500 leucocytes per cmm., chiefly of the lymphocyte type. Evidently then this case, which is otherwise similar to the first two described, differs from them in the leukæmic condition of the blood and will fall on that account into Sternberg's group of leuco-sarcomata.

The other group is perhaps more uniform in its characters.

CASE 4.—Autopsy 92, woman aged 24, in whom there was found at autopsy a large tumor mass involving the jejunum, which is enormously distended, and its walls infiltrated with the tumor, into a cavity in which the jejunum opens; apparently the tumor growth in the walls of the intestine has greatly distended the lumen and has become ulcerated within. The adjacent mesenteric lymph glands were much enlarged. The tumor tissue which infiltrates the whole thickness of the intestine is composed of a very inconspicuous stroma, with round cells averaging 8 μ in diameter. Certain round spaces in the tumor contain large pale phagocytic cells.

CASE 5.—Autopsy 225, man aged 27, showed multiple areas of tumor growth in the intestine, some of which are slightly ulcerated. There were no metastases except nodules in the liver and kidney. Microscopically the tumor tissue is rather coherent, the cells measuring 5-12 μ in diameter. The tumor growths in the liver and kidney have a distinctly infiltrative character, separating the elements of those organs.

CASE 6.—Autopsy 1842, man aged 39, showed three distinct tumor masses in the walls of the ileum, causing much distension. The tumors were deeply ulcerated but still caused great thickening of the intestinal wall. The corresponding mesenteric glands greatly enlarged by similar tumor masses fill the retroperitoneal tissues and the pelvis.

There were also nodules infiltrating the pancreas and right adrenal gland and metastases to the liver, thymus and some intrathoracic glands. The bone-marrow was dense and opaque.

Microscopically the tumor shows the same character as in the previous case, the cells averaging about 8 μ in diameter, while the interspersed large pale phagocytic cells measure about 20 μ. The pancreas and adrenal are densely infiltrated with the same tumor tissue so that their cells are widely separated from one another. It is of interest to note that a very great number of the cells of the bone-marrow, perhaps even the majority, correspond precisely with the cells of the tumor in size and staining characters. They form a very solid sort of tissue there, and among them are moderate numbers of the large pale phagocytic cells. On the whole the tissue does not look like marrow, there being so few of the cells characteristic of that tissue and the whole structure being replaced by the foreign elements. The presence of cancellous bone, however, makes the situation clear.

CASE 7.—Autopsy 2496, a man aged 57, again shows multiple areas of tumor growth in the intestinal mucosa. Patches of the mucosa were so infiltrated that the transverse folds became thick and rigid, sometimes ulcerated. The whole thickness of the intestinal wall at these areas was infiltrated with the tumor. Mesenteric lymph glands were greatly enlarged and as in the preceding case the pancreas and adrenal were spread out into great masses of tissue by the infiltration of the tumor.

The tumor tissue agrees perfectly in character with that of the preceding cases. The cells measure 8-12 μ and show no specific granulations. There are abundant mitoses. The bone-marrow is densely infiltrated with cells which resemble precisely those of the tumor in form and size.

CASE 8.—Autopsy 2543, a boy aged 7 years, of whom the organs were sent into the laboratory. In this case there were again patches throughout the intestine in which the wall of the intestine was infiltrated with the tumor cells to such a degree that the transverse folds of mucosa stood up rigidly and the whole wall was much thickened. The mesenteric glands were greatly enlarged by the same tissue growth, and as in the preceding case the pancreas and adrenals were embedded in an infiltrating mass of the tumor. In this case there were infiltrated areas in the stomach and spleen, but no bone-marrow was preserved.

Microscopically the tumor tissue is entirely similar to that in the other cases, i. e., it is composed of a very delicate inconspicuous stroma, or reticulum supporting enormous numbers of cells with large vesicular nuclei and measuring 8-12 in diameter with large pale phagocytic cells occasionally interspersed.

From an analysis of these cases the following results:

The three cases which show a mediastinal tumor growth extended to the other thoracic tissue as follows:

Pericardium	2 Cases.
Myocardium	1 "
Pleura	2 "
Bronchial glands	2 "
Pectoral muscles	1 "
Cervical lymph glands	2 "
Other lymph glands	1 "
Tonsil	1 "

In no instance was there any metastasis to the spleen, liver, or other abdominal organs. This in itself seems to confirm strongly Kundrat's idea of the regional distribution of these tumors and shows perhaps that they are not quickly spread about by the blood stream. It is curious that in one of these cases (Case 2) soft polypoid masses of the tumor actually hung in the cavity of the heart and still there were no metastases which could be regarded as due to transportation of cells by the blood stream. The extension by lymphatic channels is however apparently easy, and not only do the bronchial and cervical glands become involved, but occasionally even more distant glands. The serous surfaces may be affected by the appearance of nodules or plates in their substance, but in one of our cases (Case 3) the mediastinal mass was such that the pericardium was rendered quite rigid and the heart beat in a circumscribed cavity hollowed out of the tumor.

Histologically these thoracic tumors are seen to be somewhat different from the rest in that they are composed of rather smaller cells. Of course one cannot generalize from so few cases, but in these three cases the cells measured 5 to 8 μ, 5 to 12 μ, and 4 to 7 μ, respectively. There were in none of them the large phagocytic cells so common in the abdominal forms. It is true that Case 2, was peculiar in showing a rather

coherent tumor tissue, but otherwise it resembled the other two cases very closely.

It is surprising to find that a fairly well outlined picture is produced by the second group of cases in which the intestinal lesions form the constant feature and in which they appear to be the oldest lesions.

There are five cases, and these showed in addition to the intestinal growth lesions elsewhere as follows:

Liver	2 Cases.
Stomach	2 "
Pancreas	3 "
Adrenals	3 "
Kidneys	2 "
Mesenteric glands	4 "
Thymus	1 "
Bone-marrow	1 or 2 "
Tonsil	1 "
Testicle	1 "

In three of the cases 4, 7, and 8, the intestinal lesions formed many patches of thickening of the intestinal wall which did not produce narrowing, but rather the reverse. In these cases ulceration was not very advanced and in some of the patches it might be easily overlooked. In these places the thickness of the valvulæ conniventes which stood up stiffly, much swollen by the infiltration of cells was striking. Such prominent portions of the mucosa soon become ulcerated. In the other two cases the dilatation of the affected portion of the intestine was enormous, so that the gut appeared to open into a great cavity in a mass of the tumor. On careful examination the mode of involvement of the intestinal wall was seen to be similar to that in the other cases, although more extensive. In another case seen at autopsy in Prof. Weichselbaum's laboratory, in Vienna, the intestine throughout considerable lengths was converted into a rigid thick-walled tube. In that case the distribution of the metastases resembled that seen in this series.

In two cases there were single nodules in the liver, while in three both pancreas and adrenals were surrounded and densely infiltrated with the tumor substance. It seems probable that this affection of the pancreas and adrenals was due to extension of the tumors from adjacent affected lymph glands, but we must suppose that the cells reached the liver by the blood stream. This is true too in the two cases in which the kidneys were infiltrated, and in one with a similar affection of the testicle, and probably the involvement of the thymus in one case must also be regarded as hæmatogenous. In two cases the mucosa of the stomach was thickened by the accumulation of cells in much the same way as the intestinal mucosa.

It is generally stated that the bone-marrow is not affected, but in two of three of these cases, in which the bone-marrow was examined it was found to be markedly altered and largely occupied by cells which closely resemble those of the tumor. In the remaining three cases from the group of intestinal tumors, no bone-marrow was saved.

Histologically the members of this group agree very closely with one another. Their cells are rather larger than those of the thoracic tumors; they measured:

6-14 μ
5-12 "
6-10 " or an average of 6.6-12 μ.
8-12 "
8-12 "

There are also large phagocytic cells among the other cells in these cases, although they are not found in the three cases of thoracic tumors. It is seen from this description that there is no especial difficulty in distinguishing between the tissue from a case of Hodgkin's disease and that from a case of lympho-sarcoma; the histological characters are quite constant and quite unlike.

On the other hand although the distribution of the lesions is almost as characteristic and useful in distinguishing the two, one can imagine cases in which it might be impossible to decide definitely without the histological examination of the tissue.

It is more difficult, indeed almost impossible to distinguish the new tissue of a case of lympho-sarcoma from that in the nodular areas of infiltration or in the greatly enlarged lymph glands in leukæmia. Evidently the line to be drawn between these conditions is not a very definite one, for there are cases in which a lympho-sarcoma without leukæmic changes subsequently developed them and in Case 3, of our series there was a distinct, indeed a very great increase in the number of lymphoid cells in the blood with corresponding changes in the bone-marrow. Hence this case is probably wrongly included in the group of lympho-sarcomata according to the morphological subdivision and should properly be classed as a case of leuco-sarcoma supporting in that way Sternberg's classification.

Again there are of course many cases of leukæmia long recognized as such by the blood changes, in which there develop toward the end of life such enormous packets of enlarged glands with masses of lymphoid tissue in the liver, spleen, and other organs, that it is difficult to resist the idea that here we have to do with an infiltrating process somewhat like that in lympho-sarcoma. Even in the acute cases of leukæmia such lymphomatous nodules or areas of infiltration are found in the liver and kidney, but the destructive processes which characterise the lympho-sarcoma are absent here, the bone-marrow changes are prominent as well as those of the blood and thus the morphological distinction is made.

A subdivision of the cases of fairly typical lympho-sarcoma into two groups has been made, but it is of course not to be claimed that all cases of lympho-sarcoma will fall clearly into one or other of these groups. It is probably to a certain extent an accident that ours do so, for it is easy to see from a review of the rather confused literature, that there are many cases in which different distribution of the lesions is recorded and doubtless as stated by Kundrat any region of lymphoid tissue may be the starting point for such growths. The character of the growth and its mode of distribution is however distinctive enough, and so is its histological structure.

In contrast with this a case may be recorded in which it is somewhat difficult to settle the diagnosis in this regard.

E. E. H., man aged about 50 years. Blood count normal, great enlargement of spleen and lymph glands. At autopsy all the lymph glands, and especially those in the retroperitoneal and pelvic regions, were greatly enlarged and occupied by a dense white opaque tissue which did not completely replace the gland, but sometimes left portions of it unaltered. These nodules invaded the adjacent muscles and vertebræ and nodules appeared in the pleura, pericardium, lungs, bronchial walls, etc. The bone-marrow showed microscopically only the response to a general anæmia. The spleen enlarged and hyperæmic, showed no tumor nodules.

Microscopically the tumor consists of one type of cells, lying in a stroma. They are elongated or round or polyhedral and average 9 to 10 μ in diameter. The protoplasm of the cells is so irregular in form as to give the impression that they are coherent in a sort of tissue and not loosely arranged as in the lympho-sarcoma. The tumor everywhere has a highly invasive character. In this case there were no leukæmic changes and the bone-marrow shows only anæmic changes. Nearly all the lymph glands are however enlarged by the presence of a growth which extends through their capsules and mats them together, invading beyond into the muscles, bone and subserous tissues, but scarcely involving the organs. In this we have a sharply differentiated growth easy to outline in the involved lymph glands against the lymphoid structures, formed of coherent tissue, composed of polygonal cells and destroying instead of infiltrating the tissue into which it advances. It seems therefore that this has rather the character of a true sarcoma primary in the lymph glands than that of a lympho-sarcoma.

Such a sarcoma may in some cases resemble even in its distribution the growths which we recognize as lympho-sarcomata, but may be distinguished by their histological characters. Thus in one case there was found at autopsy a large mediastinal tumor growing almost precisely as in Case 3, and metastasising to the thoracic lymph glands, but microscopical study revealed the histological structure of an alveolar sarcoma.

The distinction which may be drawn between the true round celled sarcoma and the lympho-sarcoma depends not so much upon the histological characters of any isolated portion of the tumor as upon the determination of the point of departure of the growth, the manner of growth and the manner of distribution.

In contrast with what has been written in describing the lympho-sarcoma we find the true round cell sarcoma arising not especially from lymphoid tissue, but from the connective tissue at any point, commonly from inter-muscular tissues, periosteal or subcutaneous tissues, etc., where it forms a mass which grows expansively not from multiple or wide spread areas or origin but in one nodule which infiltrates and destroys tissue in its advance. It is much less a characteristic of the true sarcoma than of the lympho-sarcoma, to merely separate the elements of an invaded tissue without bringing about their destruction and it is therefore less common to find even remnants of the invaded tissue buried deep in the tissue of the sarcoma. The mode of growth is thus fairly distinctive in these two conditions. Metastasis takes place in true sarcomata, not so much by mere extension as by the rapid invasion of blood vessels and the production of distant nodules, strictly according to the mechanical principles of the circulation. The involvement of even the draining lymph glands is sometimes lacking, but in other cases the glands are extensively affected. These are things which help to distinguish one form from the other, rather better than the character of the cells and supporting tissue which may show great similarity in the two.

On the whole it seems possible in this anatomical way to outline clearly enough the group of lympho-sarcomata; it is only necessary however that this somewhat artificial classification be borne with patiently until the ætiological factors become known, for then we shall see clearly.

ON THE ANATOMY OF A MYXŒDEMATOUS IDIOT.

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The detailed studies of the anatomical changes resulting from the loss of thyroid function are not yet so numerous that this report will be superfluous.

The case is that of an idiot girl about 13 years of age, who for some time had been an inmate of Bay View Asylum. The history as obtained with difficulty from the Polish mother is as follows:

Ophelia P., 13 years of age. Female, white, Polish. Born of healthy parents. While mother was four months pregnant, a person died in the house. She was in constant terror till Ophelia was born, and thinks this is the cause of her child's trouble. Two other children were born later, normal, but died young. Ophelia nursed the breast and would eat articles of food put in her hands, but could not handle a teaspoon. Said "Papa" and "Mama," and seemed to recognize them, but no one else. Never walked. Mother noticed child's hair was always coarse and that she remained small. Case seen by Dr. Kirk December 13, 1904, and diagnosis of Cretinoid Idiocy made. Family was to be broken up for financial reasons, and patient put in Bay View Asylum.

Mother states child became more and more swollen. Indefinite history of thyroid treatment on entrance to Bay View Asylum. Three days before death the doctor was summoned as the child seemed to be choking up. Given thyroid gr. 1. t. i. d. Improved next day and thyroid stopped. Again worse the next day when the patient failed rapidly and died.

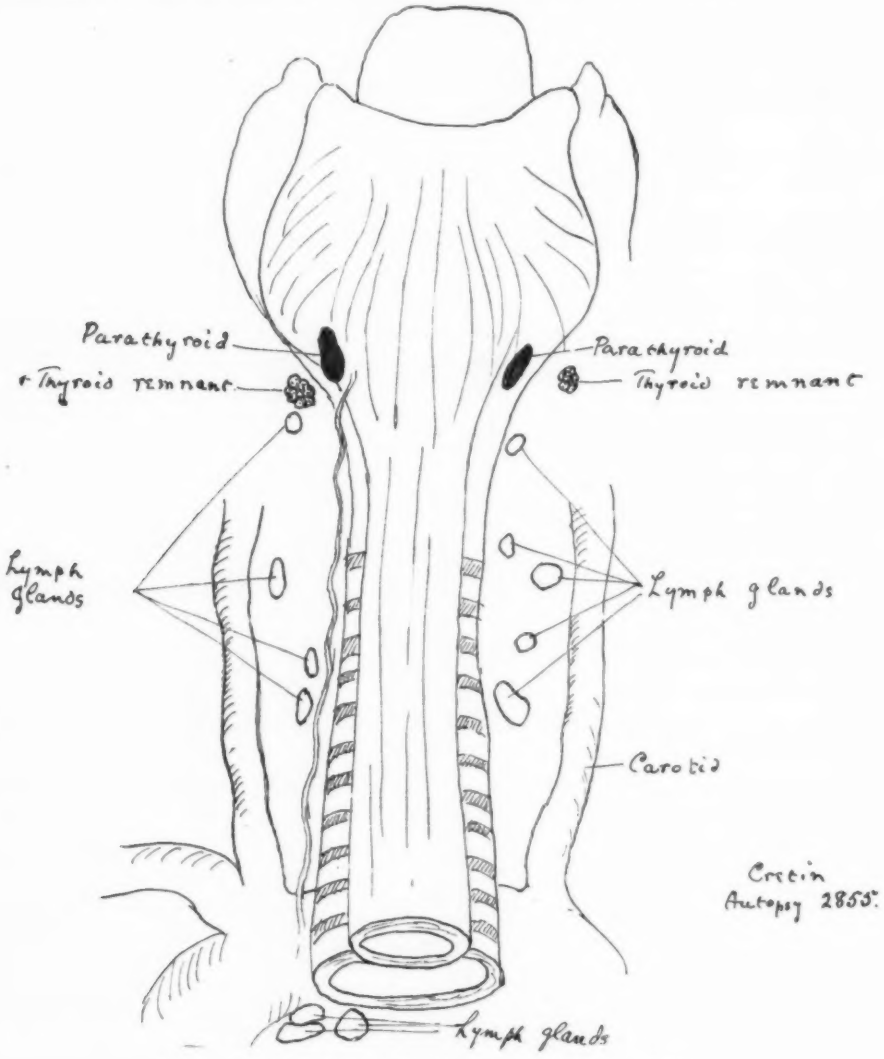

FIG. 1.—Chart of tissues of neck of myxœdematous child.

AUTOPSY No. 2855. February 27, 1907. Dr. Fabyan.

Anatomical diagnosis.—Aplasia of thyroid; cretinism; infantile condition of genitalia, etc.; hypertrophy of hypophysis; aspiration of vomitus; bronchopneumonia; diffuse hæmorrhagic pancreatitis, fat necroses; parenchymatous degeneration of liver and kidneys; focal necroses of liver.

Body is that of an extremely fat white girl, having the appearance of the body of a child six to seven years of age. The hair is cut short, but is rather sparse and coarse, especially on top. The face is expressionless on account of the large amount of adipose tissue. The forehead is prominent. The pupils are equal, measuring 4 mm. in diameter. There are no marked pads of fat beneath the eyes. The lower part of the face is puffy. The teeth are of the adult type for the most part, but are misshapen and irregular.

The supra clavicular pads are well marked. There is no sign of hair in the axillæ or about the pubes. The abdomen is very prominent and the veins stand out over the whole chest. The external genitals are small, but well formed. The arms and legs have a swollen appearance, especially on the dorsa of the feet, but nowhere is there pitting on pressure. The nails are in good condition.

On opening the abdominal cavity the fat of the abdominal wall measures 1½ cm. in thickness, and is pale and œdematous. The cavity contains 400 cc. of clear, straw-colored fluid. The intestines are of normal size and appearance, and are normally disposed, except that the sigmoid flexure has a very long mesentery and can be freely moved about. The pelvis is choked with masses of fat, which is also very abundant about the abdominal organs. The uterus is infantile in character, the ovaries apparently normal.

Pleural and pericardial cavities normal.

Heart weighs 125 gms. The pericardial surface is smooth and there is a moderate deposit of fat. The endocardium and valves are delicate and smooth throughout and the cavities of the heart contain only fluid blood. The foramen ovale is closed. The coronary arteries are delicate and the myocardium is of a uniform normal purplish color.

Lungs.—The bronchi contain considerable quantities of granular material evidently vomitus; the smaller ones are full of a bloody, frothy fluid. The glands at the hilum on both sides are enlarged, deep red, and firm. The pleural surfaces are fairly smooth, but show over the posterior part of the lungs dark purplish areas. On section the upper portions of the lungs are moist, grayish pink, and everywhere air containing, while the lower lobes, especially in the posterior portions, show on section circumscribed, slightly elevated, firm, purplish areas, which are no longer air containing.

Spleen weighs 30 gms. and measures 8 x 4½ x 2½ cm. It is of normal consistency and is of a slaty purple color, and presents a delicate capsule. On section the surface is of a uniform purple color, rather moist. The Malpighian bodies are very conspicuous as small circumscribed grayish dots. The trabeculæ are not prominent. The pulp is slightly increased in amount.

Liver weighs 830 gms. and measures 19 x 13 x 6 cm. The capsule is smooth, and the consistency of the organ normal. The lobulations are readily visible and appear swollen and pale. A few opaque areas are visible. The gall bladder contains a small amount of viscid brown bile. Its mucosa and that of the bile duct is normal.

Stomach is distended with a large amount of semi-solid food. The mucosa appears normal, as does that of the duodenum.

Pancreas measures 11 cm. in length and is of about normal consistency. The external surface presents the usual lobulation of whitish yellow color, surrounded by reddish interlobular lines. Numerous small hæmorrhages are present. Other lobules have a deep brown or purple color. There are a few scattered areas of necrosis involving fat and pancreatic tissue, the largest of these in the tail measures 4 mm. The duct contains a little gelatinous material, but opens beside the bile duct at the end of the papilla and is not bile stained.

Kidneys weigh 150 gms. The left kidney measures 8 x 3 x 3½ cm., while the right which resembles it in all respects measures 8½ x 4½ x 3 cm. The capsule strips easily, leaving a smooth surface with prominent stellate veins. The fœtal lobulations are fairly deep. The cortex on section measures 5 mm. in thickness, the striations are normal in appearance.

Adrenals are small with yellowish gray cortex and dark purple firm medulla.

Uterus measures 3½ cm. from fundus to the cervical os, while the fundus measures 2 cm. in breadth and 6 mm. in thickness. The cavity is very small but otherwise normal. The vagina seems normal. The ovaries measure 2½ x 1 cm. and are apparently normal.

Tonsils, œsophagus and *trachea* normal. There are no thyroid lobes to be found, nor is there any isthmus. The trachea is embedded in fat and loose tissue and there are no signs of either inferior or superior thyroid artery on either side. A careful dissection was made from behind and every structure charted; each gland-like body was labelled and examined microscopically with the results recorded in the chart (Fig. 1). There were found two fairly large parathyroids of normal appearance. The source of their blood supply was not very evident, but must have been from some long but very small arterial branch. They lay symmetrically on each side just at the lower limit of the larynx. No scar of any sort occupied the position normally occupied by the thyroid. Just below and outside the parathyroid on each side were found small lobulated cystic structures as charted. That of the left was filled with perfectly colorless fluid. There were several lymphgland-like masses isolated on each side in the fat near the trachea. Search underneath the arch of the aorta reveals some masses of tissue apparently lymphglands.

Aorta is normal and quite elastic.

Brain.—The skull is of normal thickness, the cerebro-spinal fluid in slight excess. The brain externally shows no great abnormality; any irregularity in the convolutions is very slight.

Hypophysis seems slightly enlarged, measures 17 x 10 x 10 mm.

The points of chief interest in the pathological alterations are to be found in the skin, adipose tissue, thyroid, parathyroid, hypophysis, central nervous system, and skeleton. The other organs showed an infantile condition but otherwise nothing especially interesting.

The skin was, as usual, rather thick and dull looking, hairs were scanty and the sweat glands badly developed. Repeated efforts to stain mucin in the subcutaneous tissue were unavailing.

The adipose tissue was extraordinarily abundant, pale yellowish white and forming not only a thick layer under the skin, but loading the omentum and other usual depots. Microscopically the fat is peculiar in occurring in fine droplets in the adipose tissue cells, instead of one large drop filling each cell.

Microscopical study was made of the two small cyst-like bodies which are shown in the chart (Fig. 1) on each side at the level of the cricoid cartilage. These were hardened in Zenker's fluid and studied in serial sections. They were quite alike, except that one, from the left side, contained an extremely small nodule of parathyroid tissue embedded in its central part. They consist as seen in the figure (Fig. 2) of several small cysts lined with flattened or cubical epithelium, and containing a loose granular sort of colloid which only partly fills each and is loaded with desquamated and pigmented cells. At one side of the cysts in each mass there is a little glandular tissue formed into acini which have scarcely any lumen. A portion of this is figured in another drawing (Fig. 3). It seems unquestionable that this is thyroid tissue, although it does not resemble the normal very closely. The supporting framework of each mass is a dense fibrous tissue in which there are occasional very small alveoli, containing colloid and lined by cubical epithelium, but most of the stroma is devoid of epithelial cells and contains only amorphous masses of brown blood pigment. Such are the very scanty remains of the thyroid lobes. There is enough, however, to suggest that the thyroid rudiment was there and from the presence of the pigment it seems clear that more tissue was there at one time but has been destroyed and has helped to furnish the pigment. It is impossible even to guess at the nature of the process. Further search was made for thyroid tissue, and serial sections were carried through all the central part of the hyoid bone, but no trace of such tissue could be found. Serial sections of the tissue in the front of the larynx also failed to reveal any thyroid tissue, but sections through the root of the tongue taken sagitally in the median line from the level of the foramen cæcum back show a considerable nodule of whitish tissue, just below the epithelial covering exactly in the position of the lingual

duct (Fig. 4). This on microscopical examination proves to consist of thyroid tissue much better preserved than that in the neck and showing numerous alveoli containing colloid, some of the alveoli are very irregular in outline, their walls being thrown up into folds so that they assume a rosette form as in the case of compensatory hypertrophy (cf. Halsted's experimental studies of compensatory hypertrophy of the thyroid in dogs). Colloid is present in the larger alveoli but is not very abundant. The epithelial cells are in general cubical, but some of them are increased in size by the enlargement of their nuclei which then take a deep stain. This is obviously actively functioning tissue differing in that respect from the atrophic nodules found in the neck, but there is in all only a nodule about 2 mm. in diameter, so small that it would have been overlooked had it not been especially searched for. The thyroid insufficiency must have been very nearly complete in this case, and the need so great that even the tiny remnant of differentiable tissue about the rudimentary lingual duct undertook the regeneration as actively as possible. No other trace of thyroid tissue could be found anywhere in the body.

On the other hand the parathyroid glands were well preserved. Aside from the minute nodule found embedded in the left thyroid remnant there was only one on each side, but these were of about normal size and of entirely normal color and consistency, being soft and flabby, and of a reddish-brown color. They lay in the adipose tissue quite free from any adhesions and apparently supplied by small arterial branches possibly from the rudimentary superior thyroid artery.

Microscopically the parathyroid tissue is normal (Fig. 5) except for the fact that it contains no eosinophile cells and that its very wide cell strands seem to be composed of compactly arranged cells with cell protoplasm which is hardly visible, with only faint granules about the margin of the cell to mark out its outline. The arrangement of the tissue is distinctly more compact than is usual in the normal parathyroid and with a low power one seems to be looking at one solid mass of cells. There is no tendency to the formation of alveoli and colloid is almost entirely absent from the gland. In respect to the preservation of the parathyroid without the thyroid, this case resembles those of Maresch and Peucker which are so well known. It seems to offer irrefragable proof of the complete independence of the thyroid and parathyroid glands and the old idea that in case of need the parathyroid which was merely an embryonic rudiment of thyroid tissue could quickly develop into thyroid tissue and replace that which was lost, is in the light of this case as of many others, obviously absurd. The parathyroids after years of thyroid insufficiency show no similarity to thyroid tissue.

The hypophysis was somewhat enlarged, its weight was not taken, but its measurements are, as recorded above, 17 x 10 x 10 mm.

Microscopically the cell masses or alveoli are distinctly larger than normal as may be seen by a comparison of Figs. 6 and 7, which are drawn under the same magnification. The individual cells are greatly enlarged and especially in most areas the chromophobe cells are elongated and radially arranged about a central lumen which often contains a minute quantity of pale staining colloid. The cyanophile cells are very abundant and form a striking feature in the section. There are some eosinophile cells but they are rather shrunken looking and by no means as distinct as in some normal glands. On the whole there is apparently a marked hypertrophy which depends upon the increase not only in the number, but in the size of the cells. The alveolar arrangement is more distinct than in the normal and the colloid production seems to be more abundant. There are some quite large masses of very pale tissue composed almost exclusively of chromophile cells arranged in large swollen looking alveoli with very small central space.

In this respect our case resembles that described by Comte (Zieglers Beiträge, Vol. 23, 1898, p. 90) in that there is an actual hypertrophy of the gland tissue. We incline to agree with him and with Boyce and Beadles as opposed to Schönemann, that the presence of the chromophile cells does not indicate any degenerative process and that the enlargement may perhaps be connected in some way directly or indirectly with the insufficiency of the thyroid. This has been suggested although, as it seems to us, not thoroughly enough studied, in the work of Rogowitsch and Stieda who extirpated the thyroid in rabbits and later studied the changes in the hypophysis which they found hypertrophied. Bayon found in his cases of cretinism an increase in the acidophile cells and in the colloid, and an increase in the density of the stroma, while Schönemann found the hypophysis in his cases of cretinism generally atrophic, although containing all the varieties of cells.

No very complete study of the central nervous system has as yet been made, but this will form the subject of a special note at a later time.

As to the skeleton which we were able to preserve and mount for study the following may be said: There is a general retardation of development and of ossification which may be best observed in the condition of the pelvis, the sternum, the teeth, etc., as well as in the size of the various bones. The skull shows changes especially in the portions forming the face which is very short vertically with prominent jaws and extraordinarily wide nostrils. The teeth are extremely irregular and both sets are represented, those of the first dentition being intercalated between the others, pushed forward or backward and much decayed. Thus of the second dentition in the upper jaw there are four incisors. The canine teeth are not distinctive while the premolars which remain are apparently of the first dentition. One large molar of the second dentition is shown on each side and on each side there is a wisdom tooth beginning to appear; there are in front of the premolar on the right side and in front of the last two molars small decayed teeth distinctly of the first dentition. In the lower jaw there are four incisors of the second dentition with four incisors of the first denti-

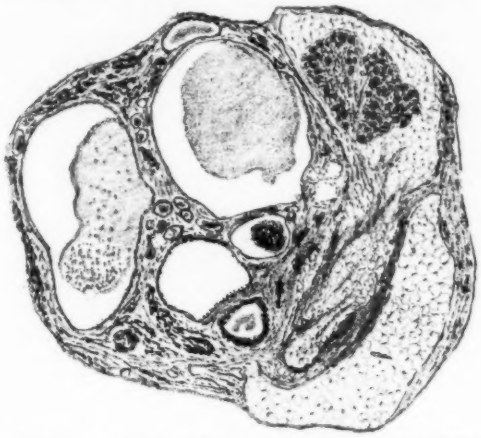

FIG. 2.—Thyroid remnant from right side showing cysts, blood pigment, and epithelial remains.

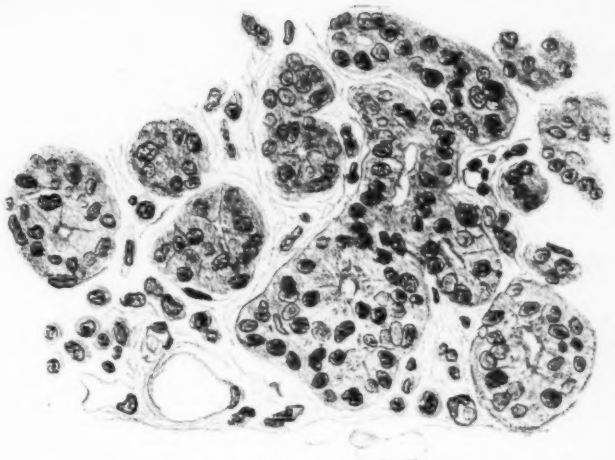

FIG. 3.—Portion of thyroid remnant shown under a lower power in Fig. 2.

FIG. 4.—Thyroid tissue on mid-line at the base of the tongue.

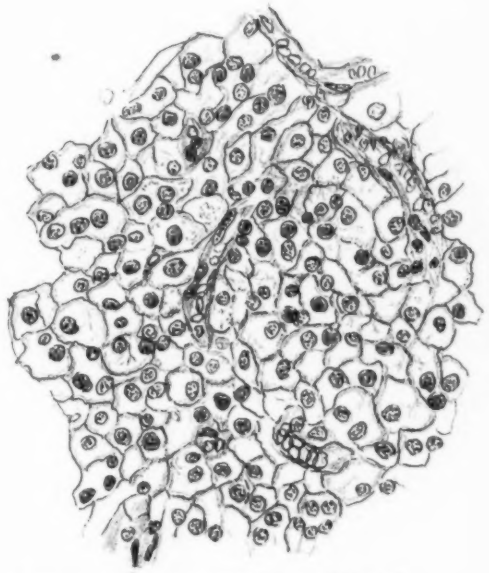

FIG. 5.—Portion of parathyroid from right side.

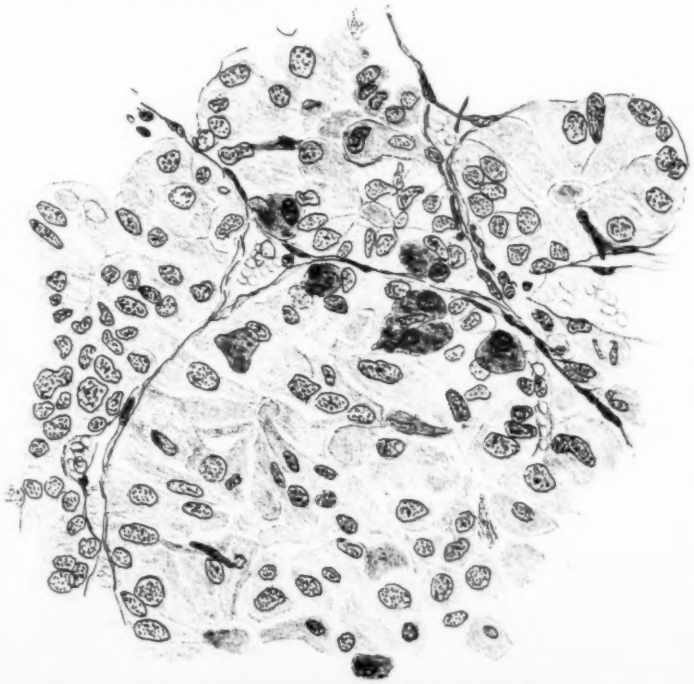

FIG. 6.—Hypophysis showing general hypertrophy.

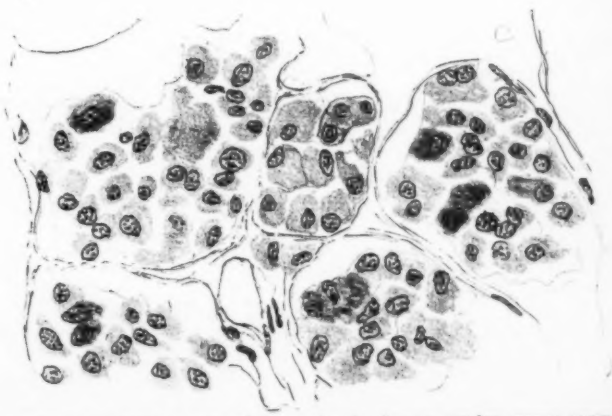

FIG. 7.—From a normal hypophysis drawn under same magnification for comparison.

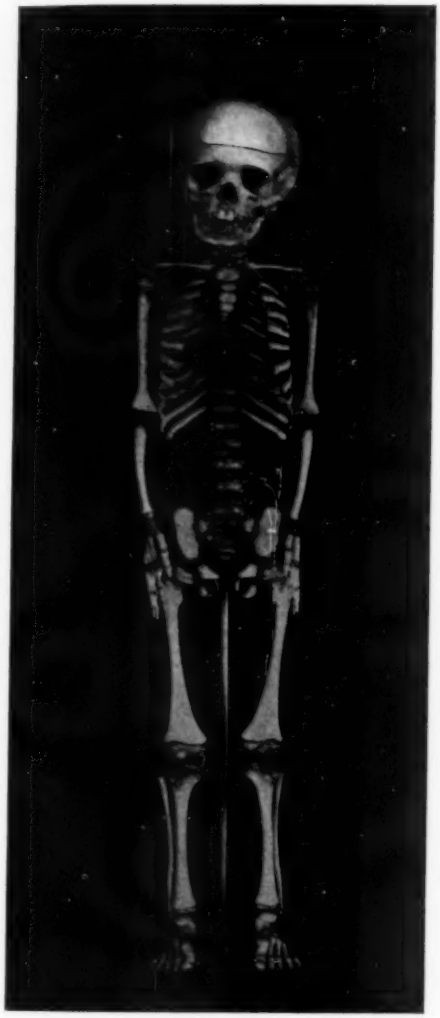

FIG. 8.—Skeleton of myxœdematous child.

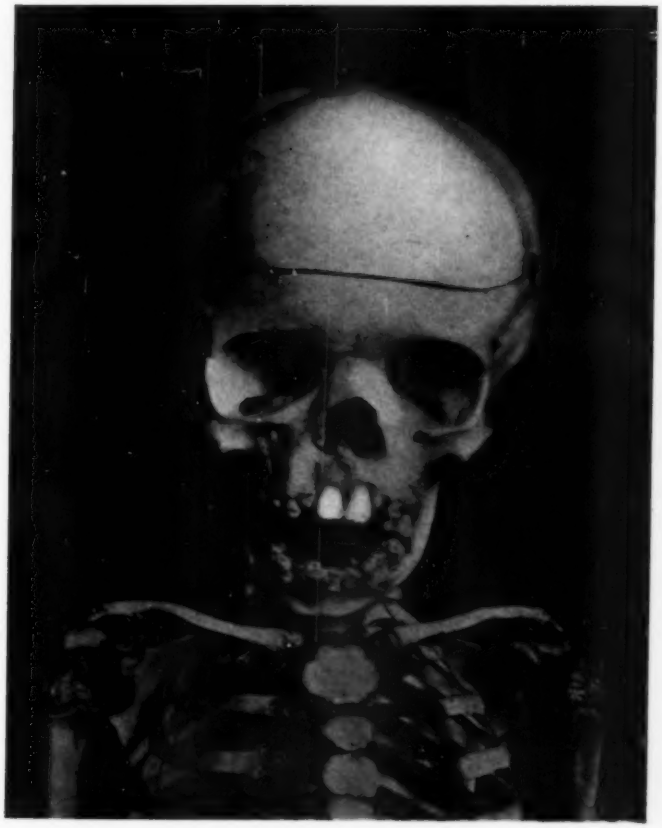

FIG. 9.—Skull of myxœdematous child.

tion still persisting but displaced. On the left there is a canine, a premolar and two molars of the second dentition with a tooth of the first dentition between the premolar and the first molar. On the right side a quite similar condition exists and on each side there is a large wisdom tooth just appearing.

The sella turcica is large, measuring 22 mm. transversely, 13 mm. anteroposteriorly and 9 mm. in depth. The spheno occipital union is incomplete and there is a very wide gap between the occipital bone and the petrous portion of the temporal. Wormian bones are very abundant.

The vertebræ seem normal in their conformation as does the whole pectoral arch.

The sternum is composed of five quite separate parts united by cartilage. The arms, legs, and ribs seem well formed, although small. The pelvis is incompletely developed for the age of the child. Normally in the 7th or 8th year the rami of the ischium and pubis become completely united by bone. In the acetabulum the three parts are still separated by a Y shaped strip of cartilage which is continuous with that lining the cavity. This cartilage begins to be ossified from several centres at about the 12th year and the union is completed from the 18th to the 20th year. In this case the rami of the ischium and pubis are still separated by 1 cm. or more and the three portions forming the acetabulum are still quite widely separated.

Measurements of this skeleton may be tabulated as follows with comparisons with the normal measurements as set down by Vierordt and Pfitzner:

	Normal Child. 13 years.		Cretin. 13 years.	
Height	135-143	cm.	96	cm.
Sitting height	71.3	cm.	56	cm.
Body weight	32-35	kg.		
	Pfitzner.			
Length of arm	60	cm.	36	cm.
Length of leg	64	cm.	42	cm.
Length of head	17.4	cm.	15.5	cm.
Breadth of head	14.4	cm.	14	cm.
Height of head	11.5	cm.	12.3	cm.
Circumference of head	50.9	cm.	47.5	cm.
Breadth of face	11.7	cm.	10.5	cm.
Height of face	9.7	cm.	8.5	cm.

Further measurements in this case are as follows:
Nostrils, 24 mm. wide. 20 mm. high.
Nasal bones, 15 mm. long.
Inner canthus to inner canthus, 22 mm.
Between outer angles of orbits, 9.2 cm.
Lower jaw, 9 cm. long, 6½ cm. transversely.
Width of thorax, 15.5 cm.
Length of thorax, 18 cm.
Sternum to tip of ensiform, 10 cm.
Humerus, 15 cm.
Ulna, 11½ cm.
Radius, 10½ cm.
Femur, 21½ cm. (Trochanter—external condyle, 18 cm.)
Fibula, 16½ cm.
Pelvis-sacral promontory to symphysis, 5½ cm.
Transverse diameter, 6½ cm.
Between crests of ilia, 12½ cm.

Langhans has pointed out that the skeletal changes in the cretin are not to be confused with those seen in the new born in cases of chondro dystrophia and further that early synostosis as a cause of retardation of development does not occur. Instead he finds an abnormal persistence of the epiphyseal cartilage and a retardation in the ossification along the epiphyseal lines. This as is seen from the above description is true to a certain extent in our case. We did not saw through the bones because of our wish to preserve the complete skeleton, but it may be seen that while the epiphyses of the humeri are fairly well ossified, those of the femur, tibia and fibula about the knee are very widely separated from the diaphyses. About the elbows and at the head of the femur this retardation is less marked.

The bones are all slender and delicate and in practically all dimensions the cretinoid skeleton is smaller than the normal, while the proportions are fairly well preserved. From this case one would be led to believe that the retardation in growth is due rather to a general disturbance of nutrition than to a special interference with one or other process of bone formation.

LEIOMYOMATA OF THE GASTRO-INTESTINAL TRACT, ASSOCIATED WITH FIBROMATA MOLLUSCA, AND SUBCUTANEOUS HEMANGIOMATA.

By Marshal Fabyan, M. D.,
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These lesions occurred in a white woman, 67 years of age. The clinical history and physical examination were unfortunately very meagre owing to the patient's sensitiveness of her appearance. She first noticed the lumps on her body when she was a little girl but had always refused to have any doctor examine her. Her husband became an invalid, and she supported him for over eighteen years by hard physical work. For eight of these years she was employed in a hospital. One daughter was born but died in childhood. The woman had always been well and never suffered from any chronic gastric symptoms. Three years before death she was removed to the almshouse, having become too weak and infirm to support herself.

At autopsy the body was found to be that of a sparely

built, old white woman, somewhat emaciated. One was immediately struck by the large number of nodular growths scattered over the whole body but especially marked over the anterior surface of the trunk. (See photograph.) A few were present on the scalp and about the ears, forehead, eyelids and mouth, the neck being especially involved. None were noticed on any of the mucous membranes. Over the extremities there were fewer nodules and the forearms and lower legs were comparatively free. The palms and soles were unaffected. The position of the nodules bore no particular relation to the course of the nerves. Their size varied from a few millimetres to 3-4 cm. in diameter, the larger ones being situated on the thighs. They were usually round or oval and quite circumscribed, but occasionally one or more coalesced, giving a lobulated appearance. Some protruded but slightly above the surface; others were elevated on a broad base and still others were supported on a short pedicle. In the main their character was sessile. Over the sacral region many of the nodules had begun to slough owing to pressure.

The skin over many of the larger was white, soft, and usually wrinkled as if a certain amount of absorption had taken place, but over the smaller, was distinctly adherent to the underlying structures. All the nodules had a uniform, moderately firm consistency and elasticity. No areas of pigmentation were observed.

On dissection of the skin the smaller nodules were adherent to the corium; others lay at the margin of the corium and subcutis, as flattened oval masses, about 1 cm. in diameter, causing no bulging of the epidermis. The larger nodules were more or less definitely circumscribed and could be readily separated from the corium and subcutis. Occasionally, they were thick enough to pass completely through the subcutis and lay on the muscle. These growths also assumed a flattened, rounded shape, extending finger-like projections into the subcutis but in some instances protruded through the corium becoming intimately adherent to it. One or two minute purplish red tumors were found in the subcutaneous tissue.

On section the nodules were smooth, firm, glistening, and translucent or slightly opaque. The larger had a distinct œdematous appearance but no fluid could be expressed. No internal structure could be made out. Those deeply situated were quite vascular.

No nodular thickenings of the larger nerve trunks or of the cutaneous nerves were noticed.

The other lesions of interest were found in the gastro-intestinal tract. The stomach was somewhat dilated and showed considerable post-mortem self-digestion. Scattered over the posterior wall in the fundus region, in an area 10-12 cm., were a dozen or more fine nodular thickenings more or less elongated, their axes being parallel to the long axis of the stomach. They bulged the peritoneal surface slightly. On section they were of a grayish white color, firm and definitely circumscribed in a few instances. The largest one measured 4 x 3 mm. The mucous surface so far as one could judge after post-mortem changes gave no evidence of their presence.

In the upper portion of the ileum a subserous nodule 15 x 13 mm. was encountered, sessile in character. The mucous membrane at its point of attachment was somewhat puckered and presented 2-3 pin-point whitish elevations beneath the intact surface. The nodule was firm and elastic, and presented on section a pinkish smooth surface composed of bundles of fibres cut in different planes.

There were no uterine myomata.

The anatomical lesions present other than those described were as follows: Arteriosclerosis; chronic fibrous myocarditis; brown atrophy of the heart muscle; chronic nephritis; emphysema; tubercular apical scar; chronic bronchitis; chronic fibrous pleuritis; anthracosis; chronic tubercular lymphadenitis (bronchial); chronic tubercles in liver; scoliosis.

Microscopically, the skin nodules were composed of masses of delicate, wavy connective tissue lying, just beneath the epidermis which had a more or less stretched appearance, the papillæ being few in number and flattened, or in the lower corium. The nodules rarely lay side by side, separated by a few strands of normal connective tissue, or one beneath the other. No definite capsule was present and although the margin of a tumor was more or less irregular, there was no distinct infiltration. A few small outlying areas proved to be separate nodules. Sweat glands, hair follicles, smooth muscle, and fat tissue were included in the growths and showed atrophy. Involvement of the sweat glands, in those superficially situated, was most often noted appearing conspicuously in the microscopical nodules.

In many of the growths, especially the larger ones, the external portion was composed of connective-tissue fibres running in a circular direction with long parallel mature nuclei and deep eosin staining cytoplasm. More internally were nuclei of the immature type, being of irregular shapes, less elongated, more oval and vesicular. These lay in an œdematous meshwork of delicate wavy fibrils which stained lightly with eosin and the connective-tissue stains (Mallory, Van Gieson). The degree of cellularity and fibrosis varied in different parts of a nodule. A few mast cells and lymphocytes were present, the latter occasionally occurring in small groups. No elastic or myxomatous tissue could be demonstrated by special stains. Blood vessels were quite numerous and larger than those ordinarly seen in the corium. The cells forming them were usually easily differentiated from the tumor cells, having nuclei uniformly large, oval and more vesicular but in some instances blended with the surrounding tissue so closely as to make the individual cell indistinguishable from a tumor cell. The nerve tissue in these nodules varied from practically none to a moderate amount.

No abnormality was noted in its structure save a rather prominent perineurium which took a much deeper red with Van Gieson's stain than the surrounding connective tissue. No microscopical lesion of the cutaneous nerves or of the larger nerve trunks was found.

A few small minute tumors lying in the subcutis were very cellular, the nuclei being large, oval, vesicular, and occasionally showing mitotic figures. The blood vessels in these were very profuse and dilated in one or two instances.

The purplish-red tumors were small hemangiomata.

The same uniformity of appearance was present in the gastric nodules as in the skin fibromata. In every instance a definite myoma was present, lying always in the outer coat of the muscularis, which gave no evidence of hypertrophy. Although in no case was a capsule present the myomatous tissue was sharply differentiated from the normal muscularis. The fibres of the latter passed on either side of the tumor and were occasionally ruptured on the peritoneal side. Each nodule was more or less elongated and composed of bundles of smooth muscle fibres arranged in irregular whorls; typical nuclei were frequently closely packed together. The intervening tissue had a homogeneous strand-like appearance and practically did not stain with eosin although markedly with Van Gieson.

The amount of this degenerated tissue varied from a minimum in microscopical nodules to an almost complete obliteration of the cellular element in some of the larger ones. The nuclei in the latter case were usually collected about the periphery. The blood supply was practically nil. In general these myomata resembled closely the ordinary uterine myoma.

The subserous intestinal nodule proved to be a myoma containing areas in which the fibrous tissue predominated. At its point of attachment to the intestinal wall the external layer of the muscularis was interrupted, the ends passing directly into the tumor for some distance, staining well with eosin. Bundles of smooth muscle cells were bound together by a small amount of connective tissue easily demonstrated by special stains. About the periphery these cells had a circular course, and a thin, fibrous capsule was present. Throughout the nodules generally were many oval and elongated homogeneous areas running parallel to the muscle fibres, and occasionally vacuolated. The muscle nuclei crossed these areas or were continuous with them, suggesting the explanation that they were due to hyaline degeneration of the muscle. The blood supply was abundant within the nodule and the vessels in the adjacent submucosa were very large and conspicuous.

In brief we have in a woman past middle life numerous fibromata of the skin associated with myomata of the gastro-intestinal tract. The other lesions present were those compatible with a person of her age.

Multiple primary tumors in one individual are not uncommon and as many as five in one instance have been reported (Ribbert). In some cases these may spring from associated tissues and may be said to bear some relation to each other but frequently different tissues are involved and there appears then to be no definite ætiology beyond a certain predisposition.

Much has been written concerning the origin of the skin fibromata. Rokitansky believed that they sprang from the deep intercellular spaces of the corium; others considered the connective tissue about the hair follicles and sebaceous glands the primary seat, while Virchow favored the connective tissue of the fat tissue as the starting point. Von Recklinghausen's observations have gone far to prove the growth to be in reality a neuro-fibroma in many instances and his work has been confirmed by Unna. The subcutaneous nodules are seen to have a more or less plexiform arrangement and the nerve tissue may be almost or entirely replaced by connective tissue. The general characteristics of these neuro-fibromata tally fairly well with the above description but there is usually involvement of the cutaneous nerves as well as larger nerve trunks which was not present in this case. In some instances where both the conditions were present the case was reported as one of fibromata molluscum associated with neuro-fibromata. In fact there is a good deal of confusion of terms and Crocker in his text-book mentions fibroma molluscum and neuro-fibroma as synonymous for fibroma of the skin. Unna considers that there is a widely distributed myxomatous change in the connective-tissue cells peculiar to neuro-fibromata which is of interest from a differential point of view. No positive results were obtained in this case and in the absence of any nerve involvement one does not seem warranted in making the diagnosis of neuro-fibroma. Ribbert favors Cohnheim's theory of embryonic cell inclusions as the ætiological factor in the condition.

The tumors here described correspond best to the so-called fibroma molluscum, a term first made use of by Bateman. All the general characteristics are illustrated here, but occasionally remnants of elastic tissue have been seen in the tumors.

Taylor has made an interesting report of the development of these nodules. There is first a slight uplifting of the skin which may have a pink color and be soft as if thinned. The prominences become round or oval, their axes tending to follow the line of the ribs on the trunk. Growth may continue slowly or the nodules may remain stationary for long periods. Those of early life are more or less gelatinous but in old age they are dense, firm and less liable to undergo involution. In rapid growth they may become firmly attached to the epidermis but later separate from it.

More advanced types may show tumors of a pendulous character, pigmentation, exotoses and neoplasms of the gums and palate. Vörmer reported a case with marked pigmenta-

tion in which microscopically a pigment fleck showed a minute fibroma molluscum. These patients may suffer from marasmus and psychical disturbances (Mayer) as well as other infirmities. Hebra considers that there is a constitutional predisposition as in many of the patients the condition can be traced to early infancy. In the case I report there was a history of early involvement of the skin, but nothing is known of the patient's family record. There was no pigmentation or mental deficiency. The progressive weakness might be explained by advancing age.

Myomata of the gastro-intestinal tract are by no means common, being very rare in the œsophagus. A myoma of the stomach wall is relatively rare and only a few cases of multiple myomata of the stomach have been reported. They are usually situated about the cardiac orifice and greater curvature (Rokitansky, Fenwick, Kidd) but may lie adjacent to the pylorus and cause symptoms of obstruction (Herford).

Their ordinary size is that of a pea, although enormous tumors have been described. Perls Neelsen reported a case in which a subserous myoma of the stomach reached as low as the pelvis and weighed 6 kilos. In some cases they have been associated with uterine myomata but this was thought to be a coincidence. None were present in this case.

The ætiology of these tumors is again doubtful, although Cohnheim's theory is usually held. The finding of aberrant bits of liver and pancreas associated with these tumors has strengthened this view (Cohn). They spring from the muscularis mucosa and on developing project toward the mucosa or peritoneum, becoming polypoid in character.

The unusual point in this case was the multiplicity of the tumors which were too insignificant to cause any derangement of the gastric functions. Furthermore, they all originated from the outer layer of the muscularis which was not hypertrophied as has sometimes been the case, giving rise to the opinion that these tumors resulted from such an hypertrophy (Ribbert, Steiner, Böttcher). In every instance the general structure resembled that of a uterine myoma; the relative amounts of cellular and fibrous tissue varying with the individual nodule, the former, as a rule, predominating in the smaller ones. In no case was there a blending of the myomatous tissue with the normal muscularis.

The symptoms arising from such tumors other than obstruction described already are chiefly due to ulceration of the mucosa with hæmorrhage which may prove fatal. As a rule, the tumors are small, slow growing and symptomless.

Various regressive changes have been noted in these myomata (Cohn). Fenwick states that the submucous type is prone to cystic degeneration, while sarcomatous changes may appear in the subserous type. Von Eising reports a case of two gastric myomata in which one was of a typical myomatous structure while the other was sarcomatous.

Intestinal myomata are not at all rare and their multiplicity is characteristic of the tumor (Mercer, Steiner). They usually lie in the lumen of the bowel. The one here described conforms to the general descriptions and requires no elaboration. The submucous type when large enough may cause stenosis and intussusception.

The interesting points of the case described are:

(a) The marked involvement of the skin with fibromata mollusca.

(b) The association of this condition with gastro-intestinal myomata.

(c) The multiplicity of the gastric myomata.

(d) The constant involvement of the outer layer of the muscularis in every instance.

(e) The presence of subcutaneous hemangiomata.

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DISSEMINATED SUBCUTANEOUS FAT NECROSIS, OCCURRING IN AN INFANT WITHOUT OTHER LESIONS.

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The case was that of an infant, born at term, of a healthy colored woman, single; 22 years old. There was a history of still birth four years before. The present pregnancy was normal but the mother had a slight puerperal infection and developed mumps two days after delivery. She was discharged well eighteen days after her delivery.

The child, a boy, was somewhat asphyxiated at birth owing to pressure on the cord, but was revived in fifteen minutes. He was well developed, being 46 cm. in length, and weighing 2970 gms. at birth. He suffered the usual initial loss of weight, but fourteen days, later when he died, weighed 3050 gms.

He was breast fed every three hours the first two days until mumps developed in the mother when he received milk ℥i with sodium citrate gr.i every two hours. Three days later the amount of milk was increased to ℥iss. The stools were composed first of meconium, then they became yellow and after being put on artificial feeding were described as white; well digested.

On the third day of life numerous so-called "abscesses" were seen on both cheeks, both forearms and on the back of the head, one buttock, and on the right lower leg. The skin over these swellings was injected. All but the abscess of the right cheek were described as not going on to suppuration and became absorbed. Two drachms of pus were obtained on incision of the swelling of the right cheek, after which healing apparently began. Cultures of the material expressed remained sterile. On the fourteenth day of life the child turned on his face while the nurse was out of the room and was suffocated. An autopsy was performed thirteen hours after death.

The body was that of a well-developed and nourished, colored male infant. The right cheek was very slightly swollen and the skin over an area just anterior to the parotid gland at a level with the upper gum was slightly purplish in color.

A pin-point abrasion was present through which the interne said only a small amount of turbid bloody fluid had been expressed the last few days. The subcutaneous tissue at this point was indurated and on incision a small softened area with a homogeneous opaque, yellowish white periphery was visible. The softened area had the appearance of tallow stained by blood; the periphery, that of typical fat necrosis. The various areas described clinically could be made out as localized areas of induration in the subcutaneous tissue which rarely caused any distinct swelling or discoloration of the skin. A marked symmetry of the lesions on the cheeks and forearms was noted. Other nodules were found on the right arm and leg, all showing a typical picture of fat necrosis. In some the central portion had begun to soften, and could be expressed on slight pressure; it was composed of a greenish yellow material. Cultures from these various areas remained sterile.

Other points noted were as follows: A few subpericardial and subpleural ecchymoses; no macroscopic areas of fat necrosis about the pancreas or throughout the abdominal cavity. The stomach was slightly dilated and contained a white smooth mass 4 x 3 x 3 cms. which had a firm elastic consistency. On section it was found to be laminated and could be torn with difficulty.

Microscopically, the pancreas and areas of fat necrosis are of interest. Many sections of the pancreas failed to show any pathological lesion. In some areas the supporting tissue was slightly œdematous, but in general the islands of Langerhans, acini, and ducts had the appearance of normal histological tissue.

Sections of the right cheek showed an area of 2 x 1½ cm. of typical fat necrosis. The tissue was involved from just beneath the corium externally to the lining membrane of the mouth. (Unfortunately, the parotid gland was not included in the specimen.) The central portion of the space was occupied by a large necrotic area without structure, surrounded by other smaller irregular ones in which the architecture was still preserved. The former contained a granular debris, degenerated fibrin, and red blood cells, including many necrotic polyblastic cells. One area of degenerated fibrin was becoming organized. In the latter smaller areas the general outline of the cells was preserved but stained a diffuse pink, the nuclei failing to stain. Many of the fat spaces had a diffuse pinkish color in which a fine network or delicate lines radiating out from a central point were observed. This radial appearance was doubtless due to spaces left by the dissolved fatty acid crystals. Surrounding these necrotic areas the normal fat tissue septa were large and conspicuous, due to a proliferation of the fixed cells together with an infiltration of wandering cells chiefly of the mononuclear type. This cellular infiltration occurred more or less grouped especially about the larger connective-tissue septa. Large round cells with vesicular nuclei and cytoplasm studded with fat globules (Opie) were also seen. Scattered through this zone were numerous multinucleated cells, the nuclei usually being collected at one pole. Occasionally, necrotic tissue adjoined perfectly normal fat tissue and in some areas the coagulative necrosis had included some of the tissue in which proliferation had taken place.

Sections from the other nodules showed a similar picture of fat necrosis with slight variations. Numerous fine pointed slits without definite arrangement were occasionally present, evidently spaces formally occupied by fatty crystals.

In some sections the outline of the fat necrosis was sharply limited, and in others the process had extended into the subcutis.

In brief we have a case in which multiple areas of fat tissue necrosis occurred in the subcutaneous tissue of a well-nourished but not obese infant, and without any apparent involvement of the pancreas. Had not death supervened by accidental suffocation clinically the prognosis in regard to what were considered multiple subcutaneous abscesses was good. Nothing in the child's condition suggested any serious disease. That the stomach at any future time could have digested the mass of curdled milk seems impossible. The natural course would probably have been a steady increase in its size by further deposits until symptoms referable to the stomach developed.

Fat necrosis has been noted many times at operations and autopsies. It is especially common in and about the pancreas, in the omentum, mesentery, and scattered more or less profusely throughout the abdominal cavity. At times even more distant involvement has been seen in the subpleural and subpericardial fat and even in the subcutaneous tissue (Chiari, Hanseman).

Autopsies on domestic animals, especially the hog, occasionally show areas of spontaneous fat necrosis (Heller, Balser, Williams).

As to the causes of this necrosis various theories have been advanced from that of Balser, who first described the condition in detail and considered it due to an over-production of fat cells, to the generally accepted view that the condition is intimately connected with disease of the pancreas. Its more frequent occurrence in and about the pancreas (5 out of 6 cases reported by Chiari) is striking and there has been much discussion as to whether the various pathological lesions found in the pancreas in these cases were not the result of the fat necrosis or whether both might not be due to some other cause. It now seems well established that disease of the pancreas may give rise to areas of fat necrosis and that given the former in any case, we are justified in assuming it to be the probable cause of the latter. That such an ætiology would also explain the occurrence of distant areas of fat necrosis has been doubted.

Various bacteria have been isolated from time to time and considered the cause of fat necrosis. Cocci and bacilli have been obtained by culture and usually identified as belonging to the commoner pyogenic or intestinal types (Ponfick). Although bacteria may undoubtedly play a part (Flexner) they probably act secondarily, the necrotic tissue predisposing to their invasion (Fraenkel).

As soon as it was suggested that certain lesions of the pancreas might cause fat necrosis numerous experiments were performed, and by injury typical areas of fat necrosis were obtained, not only in and about the pancreas and abdominal cavity, but even in the subcutaneous fat about the pubes in those animals which lived several weeks after the operation (Opie). The absence of any infection in these cases proved that the lesions may be produced independently of bacteria. Any diverting of the pancreatic juice from its normal course was usually followed by lesions in the adjoining or distant fat tissue and in all these instances the fat splitting ferment could be demonstrated (Flexner). The variety of irritants causing an acute pancreatitis on injection into the pancreatic duct was quite remarkable, even bile (Opie) and gastric juice (Flexner and Pearce) proving successful in later experiments. But in the case here described no lesion was apparent in the pancreas and we must look further for a cause.

Fat necrosis has been described as a disease entity, but Opie believes that it is always due to a pancreatic lesion. He considers that fat necrosis bears the same relation to pancreatic disease that jaundice bears to hepatic disease. However, there are cases in literature in which no lesion of the pancreas was noted. (Harrington, Körte.) Hanseman reports a case of subcutaneous fat necrosis in which he was unable to find any lesion of the pancreas except what might be considered due to post-mortem change. Flexner and Fraenkel report cases of disseminated fat necrosis without lesions of the pancreas. Gall stones were present in these cases. Rolleston considers the necrosis may be the result of a trophic disturbance of the abdominal sympathetic nerves. How this would account for subcutaneous lesions is not clear. Fitz concludes that in those cases in which the pancreas is uninvolved a primary cause may lie in the biliary tract or stomach. Whether a firm, heavy mass, as described in the stomach of this case could have given rise to the lesions seems doubtful when we consider the extensive subcutaneous involvement without internal signs. The process is considered by Chiari comparable to any retrograde metamorphosis; degeneration of the tissue being followed by simple necrosis. He has seen marked lesions of the pancreas without fat necrosis and vice versa and concludes they are not closely related.

Chiari found fat necrosis in an infant one day old with extensive syphilitic changes especially of the pancreas. This is the only other case I have been able to find in which the necrosis occured in very early life. The text-books do not consider the condition at all or speak of the diseases of the pancreas as practically unknown in infancy and childhood, with the exception of the general tissue changes such as occur in syphilis. Rotch states that the pancreatic power of digesting fat seems to be slight in the early months of life.

To sum up: In an apparently well-nourished infant we found typical areas of fat tissue necrosis.

No bacterial ætiology could be demonstrated.

No lesion of the pancreas was found nor were there lesions about the organ to suggest it.

The most advanced lesion in the present case lay in the right cheek in close proximity to the parotid gland.

Considering the fact that the parotid glands resemble the pancreas rather remarkably in structure and function, developing at about the same period of fœtal life, and that the mother developed mumps two days after the birth of the child, is it not possible that the gland posseses at this early period a lipolytic ferment which disappears in later life and

that an inflamation of the gland was the cause of the fat necrosis in this instance? The period for such extensive involvement was very brief according to evidence derived from experiments on the pancreas.

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A CASE OF PRIMARY CARCINOMA SUPERVENING IN A CIRRHOTIC LIVER.

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The lesions occurred in a colored man 62 years old. He was quite weak when first seen and could state nothing of importance in either his family or personal history. He remembered only that he had been sick a long time; his chief complaints being weakness and a swollen abdomen. Physical examination revealed a much emaciated man in whom arterio-sclerosis was marked. The thorax except for very superficial breathing and a systolic murmur over the heart's apex was negative. The abdomen was tympanitic and presented in the right upper quadrant just below the costal margin an irregular nodular prominence, evidently the liver. The liver edge was made out 5 inches below the right costal margin in the mammillary line; hepatic dullness beginning above the sixth rib. The spleen was not palpated nor were any enlarged glands made out. The patient grew steadily weaker and died one month after the first observation.

At autopsy, the body was that of a much emaciated colored man. One superficial vein on the abdominal wall was prominent but there was no marked abdominal distension. The feet and ankles showed slight pitting on pressure. On incision the abdominal cavity was found to contain about three quarts of straw colored fluid. The intestines were collapsed. The thickened and irregular edge of the liver extended below the costal margin 3 cm. in the right mammillary line and protruding beyond this for a distance of 3 cm. further was a much distended gall bladder which contained brownish viscid bile and one small stone. Marked perihepatitis was present.

A detailed description of the autopsy is not necessary and only the findings in the liver and lungs will be reported in full. The anatomical diagnosis of the other lesions found was as follows: Acute hæmorrhagic pancreatitis; arterio-sclerosis; coronary sclerosis; chronic fibrous myocarditis (calcification of muscle fibres); brown atrophy; chronic passive congestion of the viscera; œsophageal varices; chronic nephritis; chronic splenic tumor; fibroid nodules and old infarct of spleen; perisplenitis.

On lifting the heart, the inferior vena cava appeared much distended as if by a solid mass and incision disclosed a plug extending up and about 3-5 cm. from the diaphragm. It was composed of a mass of fine wavy threads 1-2 mm. in diameter forming a dense twisted tangle with many loose ends extending beyond the limits of the plug.

The liver weighed 1300 gms., and measured 21 x 14 x 7 cm. The anterior surface presented numerous nodules more or less grouped, the size varying from ½ to 3 cm. in diameter. Their color of grayish yellow and white contrasted

with the surrounding liver substance which was of a purplish red hue. A few of the nodules were distinctly green or had a purplish centre. The inferior surface also presented many groups of these grayish white nodules. None showed umbilication. Between the prominences the surface was only slightly irregular and not at all of a hobnailed appearance; the consistency of the organ was, however, distinctly increased. A red thrombus was present in the portal vein extending out of the liver some 3 cm., and into its substance for a slightly greater distance.

On section (Fig. 1) most of the liver substance, especially in the central portion and right lobe was replaced by new growth. Elsewhere the tissue was of a deep purple color, and presented numerous glistening strands of connective tissue. The new growth was arranged in rounded areas a few millimetres to 2 or 3 cm. in diameter, in many instances being distinctly encapsulated. Some were white or yellowish white; others were bile stained, especially in the right lobe and still others were of a bluish-purple color. The smaller nodules had a markedly translucent appearance which persisted in the periphery of the larger tumors. The latter usually had opaque, whitish centres and some had already begun to soften and were composed of a dry granular material.

Many of the vessels were dilated and securely plugged by a cauliflower mass of new growth (Fig. 1). In one or two of the larger vessels this advancing growth presented a blunt, circumscribed end.

Microscopically, the liver presented a thickened capsule, and a diffuse rather marked connective-tissue growth of the intra-lobular type. Associated with this was an infiltration of round cells, chiefly of the mononuclear type, and a proliferation of the bile ducts; the latter quite conspicuous in some areas. The lobules were of normal size or composd of only 3-4 cells. In some areas the capillaries were much distended with blood compressing the liver cells; in others, atrophy of the cells was present without the conspicuous capillaries, the cells being small, deeply pigmented and occasionally fatty and replaced in part by connective tissue. In others there was vacuolation of the protoplasm which stained less well with eosin, while the nucleus took a deeper color. Occupying a small portion of the same lobule or comprising considerable areas were newly formed liver cells, atypically arranged and of a much larger size than the normal cells, staining lightly and more diffusely with eosin. The nuclei were more vesicular.

In this cirrhotic liver, the cells of the new growth were arranged in rounded masses (Fig. 3), the larger ones being bounded by dense strands of intralobular connective tissue. Occasionally, a nodule measured only 12-14 cells in diameter. The periphery of such a small area might be a dense fibrous band; a delicate strand of connective tissue or the tumor cells actually join perfectly normal liver cells or those of the hypertrophied type. Although the general outline was more or less circular and fairly even, it was quite common to see normal liver cells included in tumor tissue and vice versa (Fig. 2). Some nodules were evidently of especially rapid growth and in such instances the surrounding liver cells were compressed into concentric rings, the capillaries collapsing (Fig. 3). The tumor cells were grouped together sometimes in masses, sometimes in the ordinary structure of liver tissue, but of a much coarser type; *i. e.*, the strands were several cells thick or the capillaries between them very conspicuous, almost angiomatous in character. The more usual picture was one between these two extremes. The protoplasmic boundaries of the cells were rarely distinct, and as a rule, only slightly indicated. Their size varied from that of a small liver cell to 4-6 times their size. The protoplasm of the tumor cell stained a darker, slightly purple color, occasionally showing vacuolation. The nucleus varied in size and shape. As a rule, it was slightly larger, two or three times the size of a nucleus of a liver cell, and oval (Fig. 2). The nuclear margin was distinct, the inner surface having a roughened appearance owing to minute dots of chromatin which were also scattered through the central portion, occasionally forming a delicate network. Near the centre, was ordinarily a nucleolus of irregular outline, and not always stained uniformly. The nucleus as a whole had a slight diffuse stain or was colorless save for the chromatin particles. Nuclear figures were present in great numbers and in all varieties of shapes and atypical arrangement (Fig. 4). Cells undergoing nuclear division often lay in a vacuole, and occasionally were very large with lightly staining protoplasm. A few multinucleated cells were present, and some polyblastic cells were observed among the carcinomatous cells and in the fibrous septa.

Other sections showed large areas of new growth which had undergone necrosis. The general structure had been preserved, but the whole area stained a light diffuse pink with eosin, nuclear debris being present about the periphery. Some of these areas had gone on to actual disintegration and polymorphonuclear leucocytes were in evidence.

A few nodular areas which stained lightly were found microscopically to be composed of tumor cells in which the protoplasm had been more or less entirely replaced by fine fat globules. The nuclei still retained their characteristic appearance, and were conspicuous.

Many of the portal vessels were plugged by masses of tumor cells (Fig. 5) covered in every instance by endothelium (Fig. 6). The cells nearest the centre of such a mass were often completely necrotic. No blood vessels could be made out in most of these plugs. The larger vessels contain two or more clumps of tumor cells, each with its endothelial covering.

The mass plugging the inferior vena cava was composed of numerous columns of tumor cells cut in various planes. Each mass had its endothelial covering and in many there were sharply circumscribed central necrotic areas, hyaline in some instances, becoming organized in others.

The lungs in gross were emphysematous and deeply pigmented. Lying free in the right pulmonary artery was a small tangle similar to the worm-like threads seen in the vena cava. Close inspection of the cut surface of either lung

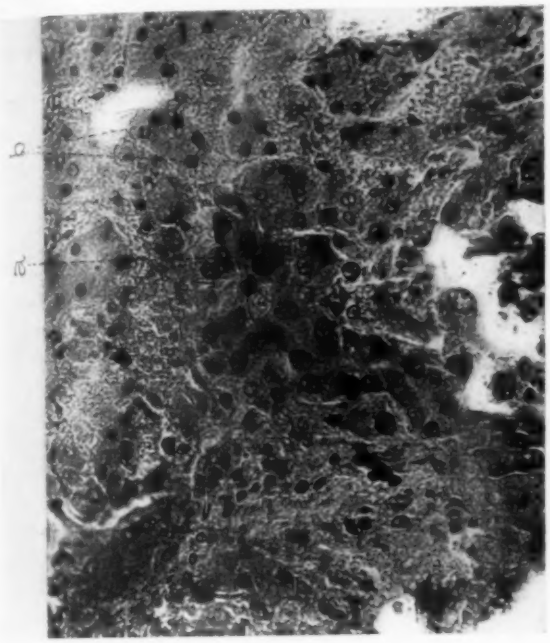

FIG. 2.—Photomicrograph. Tumor cells included between normal liver cells; (*a*) tumor cell nuclei; (*b*) liver cell nuclei.

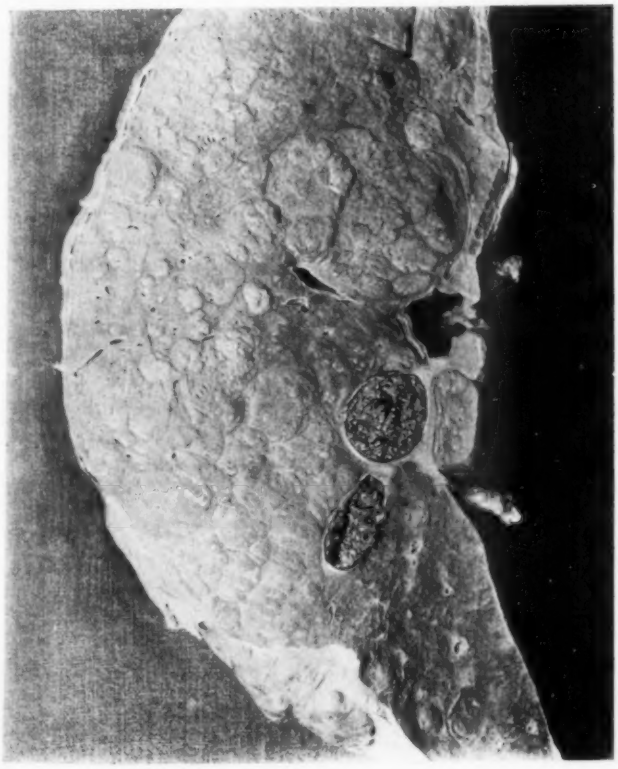

FIG. 1.—Photograph. Section of liver. Primary carcinoma.

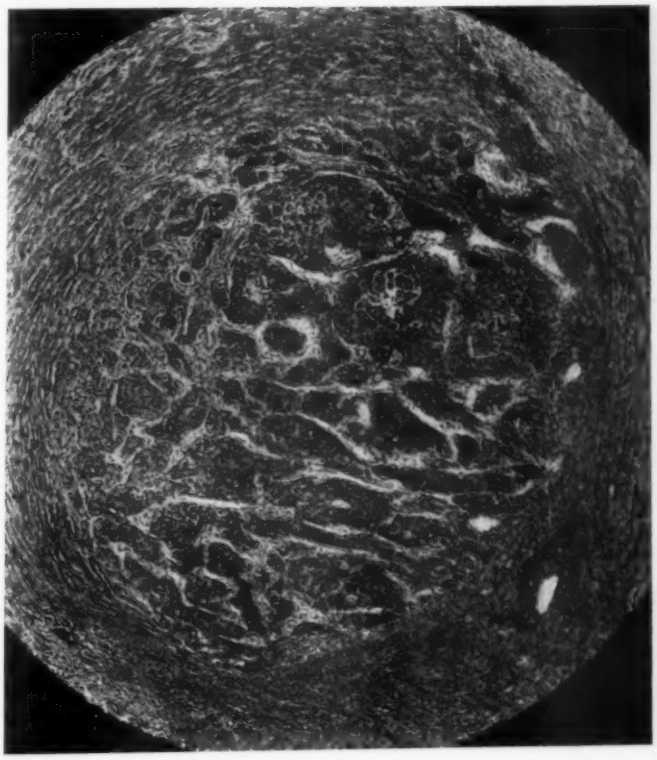

FIG. 3.—Photomicrograph. Active nodule of new growth.

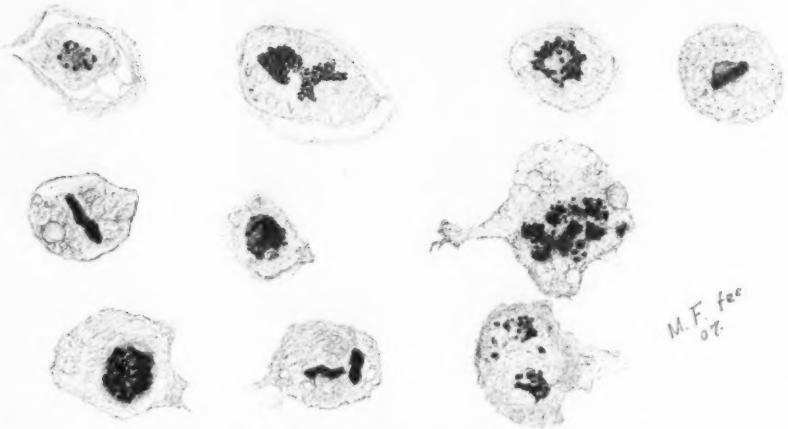

FIG. 4.—Camera lucida drawing of individual cells showing nuclear figures.

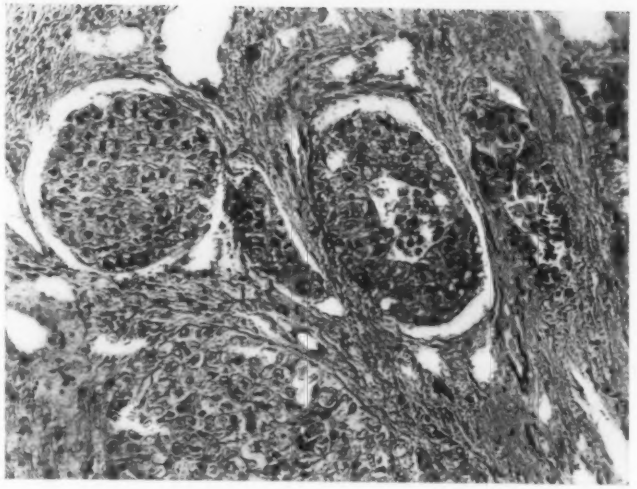

FIG. 5.—Photomicrograph. Portal vessels plugged by new growth. Cirrhotic liver.

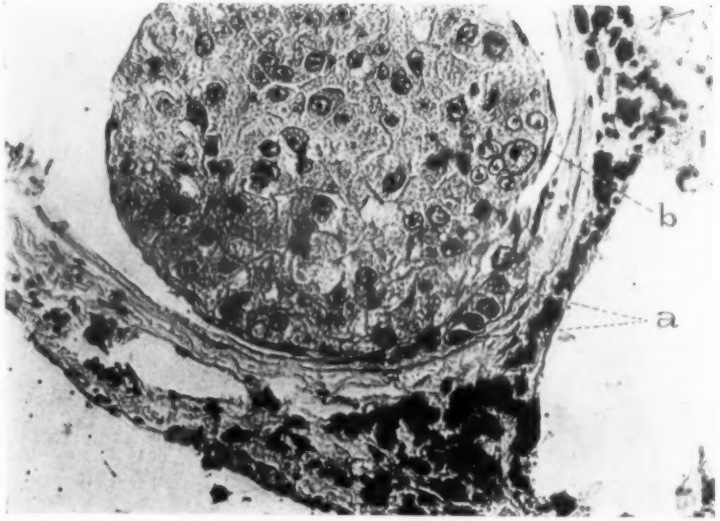

FIG. 6.—Photomicrograph. New growth plugging pulmonary vessel; (*a*) tumor cells invading vessel wall; (*b*) endothelial covering.

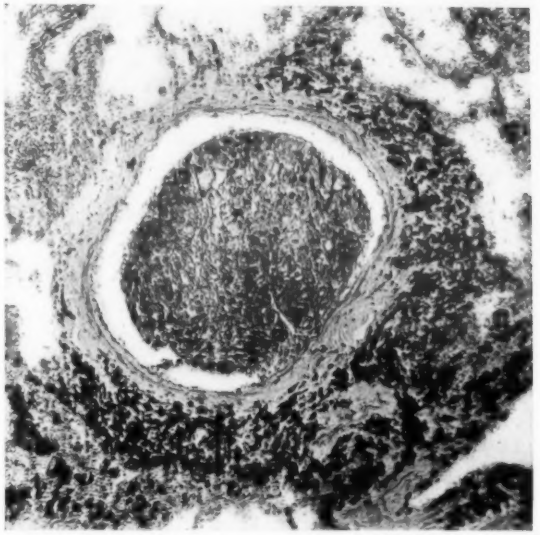

FIG. 7.—Photomicrograph. New growth plugging pulmonary vessel.

disclosed everywhere fine grayish white lines of irregular size and shape. At one point near the pleural surface of the right upper lobe were two small grayish white firm nodules 5-6 mm. in diameter, adjacent to each other. Minute dissection of the lungs failed to show any other nodules.

Microscopically, the blood vessels of the lungs were plugged for the most part by masses of cells similar to those described in the portal vessels and vena cava (Figs. 6 and 7). Mitotic figures were noted. The necrotic tissue in such a plug usually occupied the central portion, but might involve one side also. In some of the vessels the tumor cells had become a part of the vessel wall, the endothelial envelope having disappeared perhaps by a lateral necrosis as above described, and the endothelium of the vessel wall was reflected over the mass of tumor cells. Occasionally, an actual infiltration of the wall by tumor cells could be clearly demonstrated (Fig. 6).

The metastatic nodules were composed of new growth involving and filling the alveolar spaces; their walls gradually assuming the character of delicate connective-tissue septa between the masses of cells. Large areas of necrosis were present containing hyalined blood vessels. Serial sections demonstrated that these necrotic areas joined each other to form a thick worm-like mass evidently the original plug.

Several interesting points present themselves in this case, most of which have been reported in literature.

Although a careful search was made no primary focus in the gall bladder, stomach, pancreas, or rectum was found. Rolleston reported a case of secondary new growth in the liver due to primary lesion of the appendix. A primary lesion of the gastro-intestinal tract without manifestation followed by a metastasis in the liver might not be impossible, as secondary growths have been found in the inguinal glands due to continual irritation of the scrotum in chimney sweeps (Butlin). The age and sex of this case corresponds with the most frequent instances in statistics. The rather long duration of the symptoms has been emphasized in literature (White), though usually pain and more symptoms referable to a cirrhosis are present. The enlarged abdominal veins, œsophageal varices (post-mortem?) and ascites suggest the cirrhosis. Many cases of this disease have been complicated by a perihepatitis as well as gall stones. The relation of the latter to cancer has been much disputed, but properly should be discussed under cancer of the gall bladder. Although occurring frequently in primary cancer of the liver, it is generally considered a coincidence.

Aside from the general lesions which might be expected in a person of this age, the acute hæmorrhagic pancreatitis is the only unusual complication and has not been observed under similar conditions so far as I have been able to learn. The abdominal viscera were all much congested but otherwise no ætiological factor was found.

The liver in this case, as sometimes happens, was of about normal size and would not warrant a diagnosis of hobnail although the consistency proved undoubtedly that there was a rather marked degree of cirrhosis. No large tumor nodule was present and the relatively even size of the nodules would suggest multiple independent foci. The causes of such a tumor, which we will take up in a moment, would be consistent with this view, but to me it seems more probable that a larger part of the nodules must be of secondary origin; the relative ages being apparently so different. It is asserted that even the multiple foci are merely secondary tumors from a primary focus and that the comparatively rapid development of the metastatic growths gives them all a picture of similar age. In this liver there were several small nodules, which, by mitotic figures, and markedly compressed liver tissue about the periphery, denoted their rapid growth. No umbilication was noted, which is the rule in these cases, the connective-tissue element being too insignificant to cause shrinking or contracting.

The right lobe is usually most involved though in the present case the central portion was also largely involved.

The liver tissue which occupied perhaps a third of the organ showed a well-marked intra-lobular cirrhosis in which proliferation of the bile ducts and regeneration were marked.

The nodules in what might be called an early stage were composed of spheroidal or hexagonal cells arranged in columns separated by capillaries. In such areas the element of connective tissue was practically nil. In other nodules, however, connective tissue was more evident, separating the columns into islands and nests of cells. In still other areas the strands of fibrous tissue were very marked and separated even individual cells, at times giving the appearance of the type known as diffuse carcinoma, but the prevailing structure was the one first described. Other arrangements of the tumor cells have been reported (Thomson, Travis).

The number of mitotic figures was quite remarkable, a fact upon which little emphasis is laid in literature. The chromatin was arranged in innumerable fantastic shapes. Occasionally, multinuclear cells were observed, due probably to this atypical mitosis but considered by some to be artefacts (Rolleston).

The invasion of the lymphatics and blood vessels seems to be an important characteristic of this type of tumor, and though no actual invasion was noted under the microscope in this case, it has been seen in other instances. Given an invasion of the portal system with new growth, the diffuse distribution throughout the liver is easily accounted for.

Metastases into the lungs, pleura, gastro-hepatic glands and peritoneum have all been reported, the first being the most common. The presence of cells in the portal vessels is not inconsistent with a benign adenoma, but infiltration of the vessel walls and metastasis proves the malignancy of the new growth at once. I have been unable to find a case in literature in which the inferior vena cava has been so extensively plugged. It is surprising that the circulatory disturbances were so slight. The straggling ends, and loose deposits in the pulmonary artery, demonstrate the origin and path of the cancer emboli to the lung capillaries.

In the lung their growth and invasion of the vessel walls were easily seen. The necrotic areas of the metastatic

nodules which from serial sections evidently were parts of a former embolus of a vessel, suggests the earlier picture on which a metastasis has been built.

A word as to the origin of such a lesion. Various views have been set forth as to how cancer occurs aside from the general ætiology of cancer formation. In this type of case at least we have a true cirrhosis associated (Hanot), and the question arises as to what part it may play in the production of cancer. By some it is regarded merely as a coincidence (Thomson), but Muir, among others, affirms that it occurs much too often to be so considered. The cancer might be primary, with a cirrhosis resulting, but this is not borne out in cases of secondary carcinoma (Lancereaux). Eminent authorities as Hanot, and Gilbert consider that cancer and cirrhosis are together the result of some irritant, the nature of which we do not know, which works equally on the liver cells and connective-tissue cells, causing carcinoma and cirrhosis, respectively, or only one, in which case the other picture is lacking. They naïvely remark that cancer is produced much less often than cirrhosis. The more general view, however, at present seems to be that the cirrhosis is a distinctly old process on which a carcinomatous picture is superimposed. In a liver which is undergoing rapid regeneration it is not improbable that under certain conditions a compensatory hyperplasia might become atypical and assume the characteristics of a new growth. There are still those who maintain that the cancer develops directly from the liver cells (Hanot, Hunter), but equally good authorities consider there is an indirect step, the tumor cells arising from the cells of the compensatory hypertrophy (Rohwetter). This seems to be borne out by history, and morbid anatomy (Eggel).

There is a certain analogy between this condition and a chronic endarteritis which defeats itself. The occurrence of cancer in a cirrhotic liver has its analogy in the cancer developing in a chronic interstitial mastitis.

Cohnheim's views on the ætiology of cancer have to be considered and embryonic remains such as a duodenal diverticulum or an aberrant suprarenal must be thought of.

In the case here described the tumor cells resemble more closely the regenerated cells at least in respect to their nuclei, and the transition from regenerated cells to tumor cells seems less marked, though the types of cell could be differentiated without much difficulty.

On the whole, it seems as if the cancer in this type of liver was "due to an acquired habit of proliferation of the liver cells which starting as a compensatory hyperplasia gives rise to multiple adenomata eventually becoming so extensive as to constitute the cancer" (Rolleston).

The ætiology of this enormous unlimited growth of the cancer cells still remains a problem.

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A STUDY OF THE ANATOMICAL RELATIONS IN A CONGENITAL CYSTIC KIDNEY.

By F. M. Meader.

(From the Pathological Laboratory, Johns Hopkins University.)

This study is to determine the relation of the cavities in a congenital cystic kidney to the glomeruli and convoluted tubules. The material is from a fœtus described recently by Dr. Frank W. Lynch,[1] of Chicago. In so far as it illuminates our problem we shall draw postmortem details from this report. The case was pointed out by Dr. MacCallum as being suitable for our purpose; first, because of the early stage in development; second, because of the uniformly small size of the cysts.

[1] Dystocia from Congenital Cystic Kidney of the Fœtus. By Frank W. Lynch. Jour. of Surgery, Gynecology and Obstetrics, Vol. III.

The fœtus is from the fourth confinement of a colored woman twenty-six years of age. Her three children are healthy, the eldest is six years of age and the youngest three years. Twins were born at this confinement. The first that presented, the one in which we are interested, was a male, and born dead, the other was a female and lived. The dead fœtus measured 42 cm. in length and weighed 3800 grams. A meningocele 4 x 3 x 2 cm. in size protruded from the posterior fontanelle. There were sixteen teeth which were distinctly marked off and were cartilaginous in consistency. The hands were deformed; the left had a thumb and five fingers, the right had a thumb and five fingers and extending from the

FIG. 3.

FIG. 1.

FIG. 2.

palmar surface of the little finger was an accessory finger. The feet were clubbed, presenting six toes on the right and seven on the left foot.

At autopsy Dr. Lynch states that there were no abnormalities save in the liver, kidneys, ureter and bladder. The liver was cystic. The left kidney was converted into a cystic mass which weighed 1190 grams. Externally, the kidney was divided into a number of irregular areas, some of them distinctly cystic (Fig. 1).

The capsule peeled off easily. On section the kidney was semi-solid and was found to be composed of myriads of cysts, which ranged in size from several centimeters in diameter to those so small as to be perceived with difficulty. The fluid obtained from the larger cysts was of a clear serous character. The ureter was attached to the middle of the posterior portion of the tumor. At the junction with the kidney, the ureter was 1.5 mm. in diameter, and presented a patulous lumen. The right kidney was represented by a collapsed sac 13 x 7 x 4 cm. Its exterior was generally smooth, while the interior was lined by a glistening corrugated membrane, giving a honey-comb appearance. The wall of the sac measured but 2 mm. in thickness. The ureter was kinked and stenosed a few centimeters above the bladder. The bladder was empty.

The kidney was cut coronally, and half of it was hardened in Zenker's fluid, and embedded in celloidin. The other half was preserved in formalin and used as a museum specimen. Its photograph is presented in Fig. 1. A portion from the surface of the embedded material was cut 25 m. in thickness and mounted serially. Among others, a series of cysts along the course of a blood vessel was studied. In order to make the relations precise a wax model of the blood vessel and its cysts was made. In Fig. 3 the blood vessel is represented in white and the cysts in black and the numerous glomeruli are indicated by labels. The model was made 100 times the actual size. In order to study the deeper cysts, especially those near the pelvis, the remaining embedded mass was cut 75 μ in thickness and mounted serially. This also enabled us to study the coarser architecture of the kidney.

The external malformations of the fœtus suggest at once that the kidney may have structural defects, and it is found that the cortex is thickened to comprise the bulk of the kidney, while the medullary portion is entirely absent. Glomeruli are found near the calyces of the pelvis which is contiguous to the under surface of the cortex (Fig. 1). From the pelvis of the kidney thick partitions of embryonic connective tissue extend toward the surface (Fig. 2). Between these partitions may be found cone shaped or pyramidal packets (Fig. 2), surrounded by connective tissue, some of which extend with their apex toward the pelvis and base toward the surface, while others extend in the reverse direction. In the apex and for some distance down the side of the packet may be seen numerous glomeruli. About one hundred glomeruli were observed on the walls of one packet. As the tubules approach the base of the packet they increase in size and decrease in number.

The relation of the cysts to the glomeruli as found in different parts of the cortex is very interesting. Occasionally a cyst is found which has a glomerular tuft hanging from its lining wall. Clearly such a cyst is a dilatation of the capsule of the glomerulus. Frequently one found the dilatation to occur in the first convoluted tubule, while the glomerulus is normal and connected with the cyst by the proximal part of the tubule. Sometimes two kinds of cysts are connected by a small tubule (Fig. 3). There is a relatively small dilatation of the glomerular capsule which is connected by a narrow tubule with a large dilatation of the first convoluted tubule. Occasionally the glomerulus is flattened out into a tubular body, closely surrounded by its capsule, and by a slender tubule this glomerulus communicates with a relatively small cyst. Again there are numerous glomeruli with no cysts, nor even any uriniferous tubule. The glomeruli vary extensively in size. When a glomerulus is connected with a cyst at all it is found that a large glomerulus accompanies a large cyst. There was never more than one glomerulus connected with each cyst. The largest cysts have no opening whatsoever, nor have they any glomeruli, although it seems possible that their glomeruli have degenerated.

The blood vessels are not very numerous. The arteries are quite large and their walls are extensively thickened. The efferent vessels are very difficult to follow.

We were unable to find a cyst that communicated with the pelvis. In fact on dissection, the walls of the calyces were glued together so that such communication would have been quite impossible.

Some of the cysts were filled with a colloid like substance, which frequently becomes lost in making the section.

The walls of the tubules and cysts are generally lined with a single layer of cubical epithelium. In some places the epithelium is necrotic and has disappeared.

In concluding this study we might review in detail the various hypotheses which have been promulgated to explain the formation of these cysts. But these views have been so ably presented in the recent literature on this subject that our facts may be merely restated and the simplest explanation attempted.

We have a kidney which has evidently suffered disturbances in the course of its development analogous to those which produced such changes in the limbs and head. It could never have performed its proper functions for the bladder was empty and the pelvis of the kidney obliterated, and in the kidney itself the connections of the various portions of the secreting tubules are especially distorted. We find glomeruli without uriniferous tubules, glomeruli with dilated capsule but with no outlet, glomeruli opening into a short uriniferous tubule which ends in a cyst, and finally similar glomeruli connected by a tubule with a cyst, but the Bowman's capsule of which is itself dilated into a second cyst. Each cyst has only a single associated glomerulus; but there are certain large cysts, about which no remains of a glomerulus can be traced. No light is thrown on the mechanism of these changes, but the reconstruction in wax serves to make clear the nature of the anatomical relations in the kidney.

PHLEGMONOUS GASTRITIS.

By A. B. CECIL.

(From the Pathological Laboratory, Johns Hopkins Medical School.)

Phlegmonous gastritis or suppurative inflammation of the stomach wall may be diffuse or circumscribed affecting in both instances especially the submucosa. In the circumscribed form there may be a clearly defined tumor-like abscess set as it were in the submucous coat and varying in size from that of a hazel nut to that of an orange. In the diffuse form on the other hand a large part of the stomach wall becomes extraordinarily thickened by the infiltration of the layers and especially the submucosa with a purulent exudate. These conditions are regarded as primary in the stomach when no extensive area of infection elsewhere makes it probable that they are metastatic in origin. Usually the ordinary pyogenic organisms are concerned as the cause.

The diffuse form is more common than the circumscribed but both are rare. The first case described was of the circumscribed form observed by Varandaeus in 1620. The diffuse form was not described until about one hundred and fifty years later, when a case was studied by Andral and Cruveilhier. Since then a number of cases have been recorded and the literature reviewed by Raynaud (1861), Auvray (1866), Lowenstein (1874), Leube (1876), Glax (1884), Oser (1887), Ruking (1890), Mintz (1892), and more recently by Leith who brings it up to 1896 in an excellent article.[1] At the suggestion of Dr. MacCallum the remaining cases up to the present time have been reviewed using Leith's paper as a starting point with finally a description of the case which recently came under observation at the Johns Hopkins Hospital. The following cases have been described since 1896 and their characters will afford a general idea as to the nature of the process as a whole:

HUGUENIN.[2]—Painter, aged 73, illness began with attacks of pain in stomach, belching but no vomiting, pulse and temperature low; during the 11 days of illness the temperature gradually rose to 38.8° C.

At autopsy the peritoneum contained a purulent fluid with fibrin. Stomach presented a network of lymphatics distended with pus. Mucosa uniformly grayish. An old ulcer with thrombosed vessels on lesser curvature. Stomach wall markedly thickened, especially in region of the ulcer, the submucosa and musculature being especially thick and on pressure pus oozes out from them, in which streptococci are found.

The author believes that the chronic ulcer formed a portal of entry for streptococci and that the chronic gastritis weakened the activity of the gastric juice and thus allowed the bacteria to grow and invade.

HOPKINS and WEIR.[3]—Male, aged 38. Complained of pain and epigastric tenderness, vomiting of bile-stained matter. Temperature reached 104° F., pulse 120, feeble and thin. Symptoms of peritonitis preceded death.

Peritoneum contained a purulent fluid. Stomach wall greatly thickened in pyloric region and from there for about one-third of its length by the accumulation of a purulent exudate chiefly in the submucosa. There was no ulceration, but in the lesser curvature were two small abscesses which had penetrated to the peritoneum. Diplococci and bacilli were found in the inflamed tissue.

HUETER.[4]—Man, aged 61. Sick only a few hours with diarrhœa and vomiting and slight fever.

At autopsy there was a beginning peritonitis. The stomach greatly distended and roughened by fibrin. The stomach wall was greatly thickened, especially along the greater curvature, purulent fluid may be squeezed from the thickened submucosa and is found to contain cells which stain badly and streptococci together with other bacteria. There were two small ulcers along the lesser curvature and some hæmorrhagic erosions in the pyloric region which may have acted as portals of entry. In many places the mucosa and musculature are necrotic.

MERKEL.[5]—Woman, aged 45, with leukæmia treated by X-rays. At autopsy peritoneal cavity full of cloudy fluid and lined by fibrino-purulent exudate. Omentum thick and swollen. Spleen greatly enlarged. Fibrinous exudate over stomach. Fundus is normal, but the remainder is greatly thickened and doughy. Submucosa thickly infiltrated with purulent exudate laden with streptococci. Most marked infiltration was near the pyloric ring where there was a punched out round ulcer which probably acted as portal of entry for the bacteria.

KLIENBERGER.[6]—Man, aged 67, treated with iodides and calomel for various troubles. Vomiting, diarrhœa, and epigastric tenderness, later constipation during two days when death occurred. At autopsy there was general peritonitis. Omentum adherent to pylorus and infiltrated with pus. Stomach wall is everywhere about 1.5 cm. in thickness and uniformly infiltrated with pus, except for certain small abscesses in folds of the mucosa. This infiltration contains Gram staining cocci and Weigert's stain of sections shows bacteria in masses often intracellular. Author believes the iodides and calomel caused irritation of stomach and lowered resistance.

MCKENZIE.[7]—Male, aged 28. Abdominal and thoracic chest pain, nausea, no abdominal tenderness, purplish blotches over body, fever, rapid respiration, vomiting. Later great abdominal pain, tense walls, general collapse.

At autopsy peritoneal cavity contained purulent fluid. Stomach wall thickened and soft, 1.4 cm. in thickness, purulent fluid oozed from submucosa. Mucosa mottled with pink and yellow patches, lymphatics filled with purulent fluid. The infiltration of purulent exudate involves mucosa and muscularis, but to a far greater extent the submucosa. It extends a short way into the duodenum. Cultures from stomach wall and peritoneum showed Staphylococcus aureus. Author thinks the ætiological factor a gastro-intestinal infection from bad meat.

C. J. WAGNER.[8]—Man, aged 30. Chills, nausea, and pain in stomach sharply localized. Vomiting, fever, rapid pulse, collapse, and death on 10th day. Autopsy showed acute fibrino-purulent peritonitis, most intense over anterior surface of stomach, no perforation, stomach large and heavy. The wall measures 1.3 cm. in thickness and creamy pus could be squeezed from the

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[2] Rev. Med. d. la Suisse Romande, 1903, XXIII, p. 727.
[3] Brit. Med. Journ., 1904, Vol. II, p. 1406.
[4] Münch. Med. Woch., 1904, p. 85.
[5] Centralbl. f. Med. Wiss. No. 10, 1905, p. 257.
[6] Münch. Med. Woch., 1903, p. 1338.
[7] Canada Lancet, February, 1907.
[8] Canadian Pract. and Review, January, 1907, p. 12.

submucosa. Mucosa congested with superficial ulcers and infiltrated with leucocytes. Musculature and subserous tissues also infiltrated. Streptococci and bacilli found in smears. Cultures showed only B. coli and B. proteus.

SCHARROZ.[9]—Man, aged 59. No clinical history. Fresh diffuse peritonitis was found at autopsy. Stomach wall thickened to 2 cm. in pyloric region. Submucosa and musculature formed a broad homogeneous light yellow layer from which thick creamy pus oozes. Mucosa reddened and swollen, but without ulceration. Author thinks infection occurred from the tonsils, since cultures from stomach, peritoneum, and tonsils gave streptococci.

SCHMIDT.[10]—Woman, aged 70. At autopsy there was found a purulent peritonitis. There was a purulent infiltration of the submucosa of the stomach, the lymphatics being filled with exudate. There was no perforation of gastric wall, but infection extended along the lymphatics which were elevated in thick yellow wreaths. Mucosa not affected. Cultures from the submucosa and peritoneal exudate showed streptococci. Author thinks infection occurred through the mucosa although the portal of entry cannot be determined.

KONSTANTINOVITCH.[11] I. Woman, 41 years old. Fever, chill, malaise, abdominal pain, vomiting, rapid small pulse, abdomen distended and tense.

At autopsy purulent peritonitis especially about stomach. Peritoneal coat of stomach injected and through it there shine yellow opaque spots. Stomach enlarged, mucosa swollen and œdematous with many hæmorrhages. Walls much thickened from infiltration of submucosa.

Microscopically this purulent infiltration is found to invade mucosa and musculature. Veins thrombosed. Streptococci found in the stomach walls.

II. Man, aged 23. Malaise, abdominal pain, tendency to vomiting and diarrhœa, fever, rapid respiration and abdominal tenderness. Operation after seven days revealed hæmorrhagic peritonitis with gluing together of intestine.

Autopsy revealed general peritonitis. Stomach enlarged, serosa covered with exudate. Mucosa swollen and covered with punctiform hæmorrhages and shows several defects from which pus oozes. Wall of stomach thickened (1 cm.). Submucosa especially infiltrated with pus. Streptococci were found in the wall. Author believes they can invade through the mucosa even without defects of its tissue.

MAX JACOBY.[12]—I. Man, aged 24. Ill for 12 days before death. Abdominal pain, headache, diarrhœa, tympanites. No fever, intellect clouded. Right thigh hard, tender, and livid.

At autopsy a litre of yellow pus was found in peritoneum. Intestines injected and glued together by fibrino-purulent exudate. Pylorus narrow, near it the scar of an old ulcer. Stomach wall much thickened by purulent exudate which is particularly abundant about the ulcer where the wall measures 1½ cm. of which 1 cm. is occupied by the submucosa from which a purulent fluid oozes. Muscular and subserous tissue also infiltrated. Scattered over the mucosa there are several punctiform defects. Streptococci found in stomach wall and in muscles of thigh. Cultures showed streptococcus, B. coli, and B. proteus.

II. Woman, aged 24. Pain in gastric region, vomiting of coffee ground material. Abdominal tenderness, palpable tumor in midline above umbilicus. No fever, exploratory laparotomy and gastro enterostomy; death after illness of 8 days.

Autopsy.—Peritoneal cavity contained 1 litre of pus. Stomach enlarged at pylorus, a hard nodular tumor which proved to be a round ulcer 6 x 9 cm., small defects in its otherwise smooth base. Extending from the ulcer a diffuse thickening of the stomach wall due especially to infiltration of the submucosa from which pus could be squeezed. Muscular and subserous tissues also affected. Mucosa swollen with ecchymoses. Streptococci found in stomach wall. Author thinks that the phlegmonous gastritis resulted from the operation which was performed 6 days before death.

KINNICUTT.[13]—Man, aged 41. Drunken bout, vomiting, abdominal pain, fever, shallow respiration, abdominal tenderness.

At autopsy a sero-fibrinous peritonitis. Stomach wall greatly thickened by a purulent infiltration of the submucosa. A necrotic patch was found in a cicatrix near pylorus which was possibly the portal of entry of the streptococci which were abundant.

SIMMONS.[14]—Woman, aged 75. High fever and abdominal pain, death next day. At autopsy stomach wall was found greatly thickened by an infiltration of the submucosa with cloudy serous and purulent fluid, mucosa swollen but without defects. There was bronchiectasis and thrombosis of the crural veins and streptococci were found in these localities as well as in the stomach wall. Author thinks the bronchial infection primary.

CAYLEY.[15]—Woman, aged 26. Chills, headache, pain in abdomen, vomiting, constipation, fever, and rapid pulse. Abdominal tenderness, collapse and death. Autopsy revealed general purulent peritonitis. Stomach wall thickened by infiltration of submucosa, muscularis, and subserosa, smears showed streptococci and a bacillus not staining by Gram's method. Cultures show B. coli and streptococcus.

From these cases it is seen that while in some instances it is impossible to trace the mode of infection there is often an obvious source of the organisms and an equally obvious defect of the tissues of the stomach wall which might allow their invasion.

The case which occurred in this hospital recently resembles the above very closely and adds little new light to the understanding of the condition, but it may be reported on account of the relative rarity of such cases.

The clinical history obtained after death of the patient from the parents was as follows:

BERTIE H.—Female. Aged 25. Family history unimportant.

Personal History.—For past two years patient has had "muscular rheumatism" with pains in the joints and muscles at times, and for about a year has complained of pain in epigastric region and in back which comes on only after eating and lasts only a short while. Constipation, but no history of nausea or vomiting.

Eight days before death the patient went down the bay in a boat. She had not felt well for about a month, complaining especially of the pain in stomach and back. On getting home that night she vomited a quantity of greenish fluid, and went to bed complaining of severe pain in abdomen. Vomiting continued and became very frequent, vomitus was a yellow fæculent, very offensive fluid. Abdomen became extremely sensitive. Diarrhœa began and there were very frequent evacuations. Patient ate nothing, complained at times of pain. She was brought into the hospital much distended and suffering excessively from pain and tenderness in the abdomen. An exploratory laparotomy by Dr. Casler revealed an abscess between the stomach and the liver with a good deal of matting together of the intestinal loops about this area. The abscess was drained, but the patient died an hour or two later.

Autopsy 10 hours after death. Autopsy 2901.

Anatomical diagnosis.—Phlegmonous gastritis; localized peri-

[9] Wien. Med. Woch., 1905, p. 904.

[10] Dtsch. Med. Woch., 1905, XXXI, p. 287.

[11] Centralbl. f. Stoffwechsel M. Verdauungs Krankheiten. Göttingen, 1903, IV, p. 295.

[12] Ueber Gastritis Phlegmonosa, 1899.

[13] Phila. Med. Journ., 1900, V, p. 989.

[14] Münch. Med. Woch., 1901, XLVIII, p. 440.

[15] Trans. Path. Soc. London, 1902, LIII. p. 282.

tonitis and abscess formation; acute splenic tumor; degenerative changes in the liver and kidneys; lobular pneumonia; chronic adhesive pleuritis and pericarditis. Body is that of a well built negro woman. Through a long abdominal incision in the median line a drain runs down to an inflamed area in the upper abdomen. The omentum is much thickened and bound to the liver by adhesions. The peritoneum in general contains no excess of fluid. The surfaces are smooth. The stomach lies below the liver, is pale and greenish with small hæmorrhages upon its surface here and there. The abscess which was drained lay in front of the stomach above its pyloric portion bounded above and toward the median line by the liver, and matted tissues about the round ligament. The lymph glands in this region are markedly enlarged. Between the stomach and the liver which are adherent to one another, there is a second abscess cavity filled with thick turbid fluid. The pancreas is normal and there are no fat necroses. The mucosa of the duodenum is normal, and the common bile duct and pancreatic duct show no alteration. The Brunner's glands are prominent up to the normal pylorus. The stomach is not distended. Its surface is roughened by fibrin with flecks of hæmorrhage. For a distance of 1 cm. above the pylorus the mucosa is folded and easily movable. Above this it is stretched tightly over the swollen underlying tissue and cannot be moved. Throughout an area which extends for a distance of 10 cm. and involves the whole circumference of the stomach, the gastric wall measures 12 mm. in thickness. At its thickest part it is not very firm, but rather boggy, being softer in some places than in others. On the cut edge of the stomach wall the muscle layer is very distinctly visible and has a translucent greenish appearance. The subserous tissue is more opaque and dull looking, and is slightly thickened, but the submucosa is enormously tickened. It is moist, dull yellowish green and rather opaque, with slightly injected minute vessels. The injection is relatively very slight and a turbid greenish fluid exudes from the cut surface. The mucosa does not seem particularly thickened, although it is rather moist and swollen looking. There are no ulcerations visible, but minute white spots with a darker centre are scattered over its surface and are probably lymphoid nodules. The remainder of the gastric mucosa is practically normal in appearance, except for a few minute hæmorrhages. The lymph glands in the neighborhood of the stomach are opaque and swollen, and those about the head of the pancreas are particularly enlarged.

Pancreas is normal. The *spleen* is much enlarged, weighs 200 gms. The Malpighian bodies are greatly enlarged. The pulp is opaque grayish red. The *liver* weighs 1900 gms. and is of an opaque ochre yellow color. The lobules are very much swollen and very dull and opaque looking. The *kidneys* are not enlarged, they show a similar opacity in their cortex, but are otherwise normal. The remaining abdominal organs show no special abnormality. In the thorax the *lungs* are bound to the costal pleura by firm adhesions. The pericardial cavity is obliterated by similar adhesions. The *heart* is somewhat enlarged. The lungs are hyperæmic and show lobular patches of consolidation scattered throughout them.

The microscopical examination of the stomach shows that the thickening of the stomach wall is due to an extraordinary infiltration with a purulent exudate. The mucosa is practically normal, there being only a slight abrasion of cells from the most superficial portions of the glands. There is a slight infiltration of the muscularis mucosa, but beneath this the submucosa is rendered unrecognizable by the very wide separation of its tissue elements by the exudate. The blood vessels are spread wide apart and many of them are thrombosed. The lymphatics are enormously distended with fluid and cells. The connective tissue fibres are spread wide apart by the exudate which consists of fluid, fibrin and leucocytes. The fibrin forms a very delicate network. The cellular elements are for the most part polymorphonuclear leucocytes, but there are also some mononuclear cells; most of them are fairly well preserved, but in places they have lost their nuclei and are disintegrated. Where the cells are most closely packed the disintegration is most marked and here apparently the bacteria are collected in the greatest abundance. The muscularis is also greatly thickened by the separation of the muscle bundles by quantities of fluid, fibrin, and leucocytes. The exudate is here of quite the same character as in the submucosa and extends through to the subserous tissue which is also much thickened and is limited by a dull layer of fibrin which covers its peritoneal surface. (Fig. 1.)

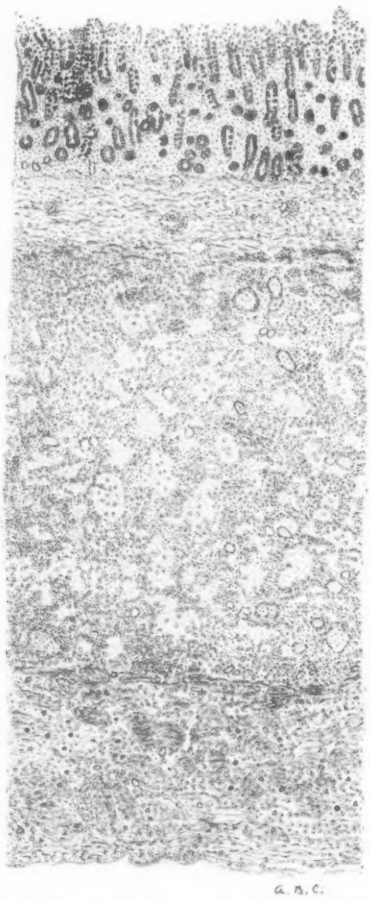

FIG. 1.—Section of stomach wall. Prepyloric portion of greater curvature.

Bacteriological examination.—Smears were made from the purulent fluid oozing from the stomach wall and stained by various methods. These smears show a number of bacilli, usually in pairs together with a much larger number of smaller organisms, somewhat lanceolate in form about the size of the pneumococcus and occurring in pairs. These stain very badly and many of them seem to be mere shells, in other instances they look like bacilli with polar staining, and a clear space in the centre. The paired bacilli described are quite stout and stain very brilliantly. Sections of the stomach wall stained by Weigert's method show only one type of organism, but those are present in enormous numbers, both inside the leucocytes and free. These stain well for the most part, but some of them are mere shadows as seen in the smears. They are diplococcus forms, sometimes somewhat lanceolate in form, sometimes almost like short bacilli. In some instances the resemblance to a polar staining bacillus is again

evident. No large bacilli are seen in the sections stained by Weigert's method. No chains of cocci nor clumps can be made out. They are practically always in pairs. Cultures were made with extreme care from the stomach wall upon agar and in bouillon, but the colonies which appeared proved on examination to be colonies of the Bacillus coli communis. There are one or two colonies of a non-Gram staining sarcina, but no colonies of cocci appeared. Several of the plates showed only uniform colonies of the Bacillus coli communis. It is extremely unfortunate that the bacteriological study is so unsatisfactory in spite of the care taken to make successful cultures. It seems probable that the colon bacilli were secondary invaders, and that the coccus forms which failed to grow in the cultures formed the actual causative factor.

ON THE OCCURRENCE AND PHYSIOLOGICAL NATURE OF GLANDULAR HYPERPLASIA OF THE THYROID (DOG AND SHEEP), TOGETHER WITH REMARKS ON IMPORTANT CLINICAL (HUMAN) PROBLEMS.[1]

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INTRODUCTION.

In taking up the study of so complex a problem as goitre, it seemed to me that human material could not be given primary consideration on account of the maze of complicating and perplexing conditions through which to interpret one's observations.

The dog and sheep were chosen as the animals most suited for the study of fundamental problems for the following reasons: They offer abundant and readily accessible material, complicating conditions are reduced to a minimum, experimental control is easily maintained, and lastly, as regards their food, these animals represent types to which man is intermediate. The next step was to establish a point of departure—a base line so as to speak. For this purpose *anatomy* seemed to offer the most satisfactory and constant base. My material has thus far consisted of 352 dogs' thyroids and parathyroids, 35 sheeps' thyroids, 31 bovine thyroids, and 173 human autopsy specimens, and preparations from as many other animals as opportunity afforded.

Concerning the term "Glandular Hyperplasia"—exactly what is meant? It is a descriptive term not susceptible of so varied an interpretation as is the term "Goitre," and by it is meant the occurrence of all grades of changes in the thyroid characterized by the production of columnar types of epithelium with the intra-acinar, papillomatous invaginations, by the hypertrophy of the stroma, by the increase in the blood-supply, and by a decrease in the stainable colloid. It may or may not be (as the name implies it generally is) associated with the formation of new acini. There are all grades of these changes ranging from the normal cubical gland cells to that stage where there is no longer any resemblance to thyroid at all, sections appearing as solid epithelial fields without acinar lumen or colloid. Histologically it is the same condition that Halsted (1) produced in normal dogs' thyroids by partial excision and which has been fully described by him and Welch (2).

DISTRIBUTION AND INCIDENCE.

This condition of the thyroid is spoken of by the physicians and laymen as Goitre. It is one phase or stage of goitre. It is very common (endemic) throughout the region of the Great Lakes from Montreal to Duluth (3, 4, 5), though its incidence, clinically at least, varies in the different districts, *e. g.*, in Buffalo and Detroit one sees a greater proportion of the animals affected than in Chicago. In the district of Cleveland about 90 per cent of all the street dogs show the glandular changes on histological examination. Sheep are affected to about the same extent, especially in the Lake Erie slope of Michigan and Ohio. Cattle are affected but apparently to a lesser extent. Exact limitations of this area are important, particularly to ascertain whether it is confined to the region of glacial drift or not. Clinically at least goitre is diminishing in frequency in the region of the Lakes as is true in all goitrous districts (6, 7). This is especially true of the sheep in Michigan, where some 15 to 20 years ago the future of the industry was a serious consideration on account of the number of cretin lambs, but now it is gradually disappearing. Acclimation and the more extensive use of iodine-containing salt have undoubtedly been great factors in its disappearance. Well cared-for dogs show a greatly lessened percentage of glandular hyperplasias. Of the animals below the mammalia, I am not prepared to make a statement.

ANATOMICAL DESCRIPTIONS.[2]

(1) *The normal gland* for all mammalia shows only minor histological differences—the herbivora generally having a more prominent stroma. In the dog the normal gland does not exceed 0.300 gm. per kg. of body weight. The gland capsule is thin. The vessels are small. In color the gland is pale, yellowish-gray, and translucent. On section it is firm, rubbery, and one can see the acini filled with clear honey-colored colloid of a thick syrupy consistency. Microscopically the acini are rounded, slightly variable in size and with regular walls. There are no intra-acinar twigs or pro-

[1] Presented at the meeting of the American Association of Pathologists and Bacteriologists, May 9, 1907, by Dr. R. G. Perkins.

[2] Technique: In all the histological work four per cent formaldehyde solution has been used as the hardening reagent because the metallic salts so fix the colloid as to render sectioning at 10 to 15 microns with the celloidin method very difficult. The tissues were imbedded in celloidin and the sections were stained in Delafield's hæmatoxylin and two per cent yellow eosin.

jections. The stroma is scanty and supports very small blood- and lymph-vessels. The epithelial cells lining the acini are regular, low cubical, with small darkly staining nuclei, and are arranged in a single layer. The stainable colloid is dense, homogeneous and stains uniformly. It sharply abuts on the epithelial cells. Adjoining acini may show colloid of different staining intensity—a condition that has been attributed to a possible variation in the lymphatic drainage.

(2) *The glandular hyperplasias.*[3]—Here the changes are similar to those occurring in primary (exophthalmic) toxic goitre in man and are identical with those described by Halsted (8) following partial excisions of normal dogs' thyroids. Of this type, as mentioned above, there are all graduations from the normal gland to the most extreme change in which there is no resemblance to thyroid at all.

This change may be briefly described as follows: The gland in the main shows enlargement proportional to the degree of glandular hyperplasia. In a moderate example, the thyroid lobes are enlarged uniformly and symmetrically. The capsule is thick and the vessels are much enlarged and tortuous. The lymphatic trunks leaving the gland are enlarged and if exposed during life are most striking for their size, and are filled with rather clear lymph-like fluid. On section the tissue is very vascular. It has a fleshy, opaque, gray-red appearance and a finely granular cut surface. There is no visible colloid. Microscopically the stainable colloid is greatly reduced or absent, there being in its place only a small amount of pink granular material. The acini show extensive papillomatous ingrowths and invaginations of their lining epithelium, more or less effacing the acinar lumina. The epithelium is high columnar in type and arranged in a single layer. The epithelial nuclei are large, pale, round, vesicular, and basal. The cytoplasm is quite granular. The stroma is diffusely increased, contains numerous, large blood and lymph channels and occasional small collections of lymphoid cells.

(3) *Simple colloid goitre.*—The changes noted in uncomplicated forms are briefly as follows: Generally speaking they may be designated as exaggerations of the normal structures of a normal gland. There is uniform and symmetrical enlargement of the lobes. The capsule and blood-vessels are moderately enlarged and thickened, the blood-vessels as a rule showing very much thickened walls (a process of physiological obliterating endarteritis similar to that occurring in the involuting uterus), while the lymphatics are barely noticeable in the gross. On section the acini are large, well defined, and filled with dense uniform colloid with occasionally some blood pigment. (Hæmorrhage into the acini in the marked glandular hyperplasias is very common, and one frequently sees the surrounding epithelial cells filled with the blood pigment and it is not unlikely that the old pigment occasionally seen in the colloid stages represents the unabsorbed portion.) The tissue has a clear, translucent, yellow-gray appearance and is not vascular.

Microscopically the colloid stains uniformly and densely, and sharply abuts the epithelium. The acinar walls are often reduced to mere lines and in some glands there seems to be no increase in the inter-acinar framework—indeed it may seem diminished. In most colloid glands there are to be seen more or less numerous sprigs or twigs of acinar walls jutting into the acini, that are probably in part remnants of ruptured acinar walls, but, as will be shown later, are for the most part the remnants of the infoldings and invaginations of the epithelium as described under the glandular hyperplasias.

The following table of analysis of 202 dogs' thyroids gives a summary of the changes according to the structure and to the degree of change:

[3] While this paper deals particularly with the changes in the thyroid gland, it must be borne in mind that the animal, whether man, sheep, or dog, shows changes in other tissues that are equally as striking and are probably of equal importance.

These changes occur particularly in the lymphatic system, including the spleen and thymus, and are associated with varying degrees of chlorotic anæmia and changes in the blood picture.

In the case of the thymus, it is usually persistent and often enlarged. The spleen is also enlarged (in children frequently palpable) and histologically there is a general increase in the fibrous framework associated with great prominence of the Malpighian bodies. The lymph glands are universally enlarged, but show all degrees of hypertrophy from the slightest prominence to cases clinically simulating Hodgkin's disease as described by Warthin (9). Histologically they show a general increase in the stroma and also in the lymph-centres. The bone-marrow also shows changes of varying degrees that are not separable from those found in lymphatism. All these changes in the lymph and hæmatopœtic tissues are reflected in the blood picture. Dr. L. W. Ladd (10) tells me that for the human the main changes found in the blood are a reduction in the hæmoglobin and an absolute and a percentage increase in the mononuclear elements, which may be from 30 to 45 per cent of all white blood cells.

From this synopsis of the changes in other tissues, it can be seen that this subject has very important and intimate association with the condition called lymphatism or status lymphaticus on the one hand and with toxic (exophthalmic) goitre on the other. As is well known lymphatism shows distinct district limitations (Vienna, Cleveland) which for the most part are within the limits of endemic goitre. This leads to the question whether lymphatism should not represent a group of conditions characterized by varying degrees of lymphatic enlargement together with changes in the thyroid, occurring in animals, instead of being applied to those few individuals dying from some trivial cause, in which at post-mortem there is a persistence and marked hyperplasia of the lymphoid tissues. Then, too, a word as to syphilis in relation to this group of conditions. It is my opinion that syphilis has been unduly blamed for these changes in the human and that there is a great group of lymphatic enlargements in which syphilis plays no ætiological rôle whatever. This view is further strengthened by the fact that dogs, sheep, and cattle show the same changes that occur in man and iodine seems even more efficient in its treatment.

(It would be important to know whether iodine is stored in the lymph glands as well as in the thyroid and the thymus following its administration.)

TABLE OF ANALYSIS OF 202 DOGS' THYROIDS.[4]

Glands—size of:	
Normal	112
Slightly enlarged	52
Much enlarged	38
Capsule:	
Normal	108
Slightly thickened	61
Much thickened	33
Vessels:	
Normal	101
Slightly enlarged	66
Much enlarged	35
Stroma:	
Normal	64
Slightly increased	93
Much increased	45
Stainable colloid:	
Normal	49
Increased	18
Reduced (all degrees)	117
Absent	18
Alveoli:	
Normal	34
Distorted by papillomatous ingrowths—slight	45
moderate	44
marked	69
Increased in size	20
Alveolar epithelium:	
Normal (low cubical)	31
Uniform cubical	41
Low columnar	61
High columnar	69
Desquamation	33
Cell nuclei:	
Normal (small dark)	65
Moderate size, pale vesicular	19
Large size, pale vesicular	118
Glands—condition of:	
Normal	19
Colloid hypertrophy	15
Glandular hyperplasia (all degrees)	168

THE PHYSIOLOGICAL NATURE OF THE GLANDULAR HYPERPLASIAS.

From a careful study of the material, experimental and anatomical together with the available literature, I think the most rational conclusion is that it is a *physiological reaction* on the part of the gland to a demand from the tissues, and that these glandular changes are to be considered *cretinoid* in nature.

The following evidence may be cited:

(1) Clinically, dogs manifest all degrees of the symptom-group from true cretins to normal dogs.

(2) It affects the young and they tend to recover spontaneously.

(3) One can produce the same histological changes in puppies by partial removal of the glands from the mother before pregnancy.

(4) The same changes can be produced in normal dogs' thyroids by partial removal.

(5) The hyper-activity of the gland is evidenced by the tremendous increase in the blood-supply and the distended lymphatics.

(6) Anatomically there are all degrees of the reaction from the comparatively normal gland to the most marked glandular change. Taking up the assumption that these glandular changes represent stages in a physiological reaction to a deficiency as the most natural deduction from the observed phenomena, the question arose: What might this deficiency be, against which the gland was reacting? *Iodine* naturally was the first suggestion. The importance of iodine in the body economy is ill understood and I felt that further advance in the study of the thyroid would be hampered until the rôle and mode of action of iodine was better understood.

The fact that iodine is a normal constituent of the thyroid gland and that it is practically a specific remedy in endemic goitre suggests that it plays an important part in the normal physiological activity of the gland. In support of this view, the following data may be cited:

(1) The iodine content varies inversely with the degrees of glandular hyperplasia.

(2) Iodine or iodine containing compounds will reduce this glandular activity in the dog in all cases.

(3) Iodine will prevent the occurrence of glandular hyperplasia after partial removal of normal glands which would otherwise hypertrophy.

(4) Iodine will prevent the occurrence of hyperplasia of the thyroids of puppies from bitches in which three-fourths of the gland has been removed.

(5) Endemic hyperplasia of the thyroid does not occur along the seacoast. MacCallum (11) finds that about 7 per cent of the dogs' thyroids in Baltimore show glandular changes as compared with 90 per cent in Cleveland.

RELATION OF GLANDULAR HYPERPLASIA TO THE IODINE CONTENT.

It was early suspected that there might be a direct relationship, because Baumann (12) and Oswald (13) had shown that in general the iodine content varied directly with the amount of colloid (thyreo-globulin), and Oswald had further observed that in general the amount of stainable colloid varied inversely with the degree of glandular hyperplasia, therefore on these premises one could prophesy that the iodine content would vary inversely with the degree of glandular hyperplasia. This is exactly what is found to be the case. W. W. Williams (14) has shown that in general one can predict the condition of the epithelium from the iodine content of the gland. We have further shown that iodine is stored in the thyroid with great rapidity when fed to dogs and that it disappears from the gland very slowly.

EFFECT OF FEEDING IODINE CONTAINING COMPOUNDS ON THE THYROID GLAND AND ON THE ORGANISM AS A WHOLE.

The administration of iodine containing compounds to

[4] Cleveland Med. Journ., February, 1907.

dogs quickly (two to three weeks) induces a reversion of all the gland structures to a more normal type. I have followed this process step by step and parallel with the administration of known quantities of iodine, having first removed a control lobe from the dog and at intervals removing bits of the remaining lobe. The changes observed may be summarized as follows:

(1) Marked reduction in the size of the gland as a whole.

(2) Reduction in the blood-supply associated with obliterative endarteritic changes similar to those occurring in the uterine vessels during involution.

(3) The acinar epithelium reverts from high columnar to flat cubical. (This may take place in two weeks.)

(4) There is a rapid accumulation of normally staining colloid.

(5) There is a great increase in the iodine content of the gland over that of the control lobe and even over the normal content of a normal gland.

(6) The lymphatics instead of being the huge, sacculated trunks filled with rather clear watery fluid become barely noticeable.

The dogs' general condition undergoes equally striking changes. That is from a wizened, a sleepy, listless, rhachitic creature, he changes to an active, robust healthy dog.

Feeding fresh or desiccated sheeps' thyroids, however, often induces serious and toxic effects—a point that will be referred to later.

Relation of Iodine to the Body Economy.

The evidence brought out by the above experimental work, together with that found in the literature shows that iodine plays a remarkable rôle in the body metabolism (15). The work thus far does not exclude the possibility that iodine may be a specific remedy for an infecting agent operating in these cretinoid conditions. It does, I think, offer an adequate explanation on a physiological basis for all the observed phenomena.

Indeed there is reason to believe that the body economizes iodine much as it does iron, and to carry the suggestion further there is reason to believe that iodine is related to endemic goitre much as iron is to chlorosis. Both conditions are probably vastly complex, but these two elements (iodine and iron) may be the nuclei around which their metabolic complexities are grouped.

If iodine does play such an important rôle in the body metabolism its distribution in nature and in animal foods is important to ascertain. As to where this iodine deficiency exists I do not know. It might be in the food, in absorption, or in assimilation.

Relation of the Glandular Hyperplasias to Cretinism.

As before remarked I think the different degrees of glandular hyperplasia represent different stages or degrees in the cretinoid condition. The word "cretinoid" as used by Gull (16) is not exactly descriptive here, for while there is every reason to believe that these glands have a *hyposecretion* physiologically, yet *quantitatively they have a hypersecretion*, and this excess of an abnormal secretion produces certain toxic manifestations not unlike those seen in Graves' disease. If the deficiency is not met there is, as pointed out by Ord (17), a gradual destruction of the glandular tissue by fibrous overgrowth and subsequent loss of gland function.

Relation of Glandular Hyperplasia to Colloid Goitre.

The ease with which all cases of glandular hyperplasia in the dog revert to a colloid type upon the administration of iodine containing compounds suggests that colloid goitre is the quiescent stage. In other words, in its simplest form and conception, glandular hyperplasia is the hyperactive stage of the cells, and colloid goitre is the quiescent stage after the deficiency has been met. Whether this is the only mode of production of colloid goitre in the dog or sheep I do not know. It is the only form I have met with and certainly is the most important. It would seem that a purely passive dilatation of the acini would be possible, but for the determination of this point human colloid goitres could not be used because as we see them in the laboratory secondary changes or complications are present in all.

If this interpretation of the formation of colloid goitre be the correct or usual mode, then the term "colloid degeneration" as applied to colloid goitre is a misnomer.

Applications of These Findings to Important Clinical Problems.

Their bearing on the commercial preparations of the thyroid gland.—The nature of the active principle of the thyroid is, in all probability thyreo-globulin (colloid). This is the view advanced by Baumann (18), and Oswald's (19), Gauthier's (20), and Wells' (30) work upholds this view and it is accepted by most physiological chemists. As before mentioned, the iodine content varies directly with the amount of stainable colloid and also inversely with the degree of glandular hyperplasia in the dog and sheep. This being the case, desiccated thyroid made from these hyperplased sheeps' thyroids must also vary greatly in the amount of stainable (colloid) thyreo-globulin. Acting on this deduction I have found that these hyperplased sheeps' thyroids, whether fed fresh or dried, have a highly toxic action on cretin dogs. The main symptoms produced are: Increased appetite at first, rapid emaciation, progressive weakness, diarrhœa, tremor, and death. Normal dogs are more resistant. In feeding the commercial preparations, the same toxic effects are produced, but as a rule are less marked and different preparations show considerable variation in their toxic and their beneficial effects. I have lately had occasion to visit some of the larger commercial laboratories and find considerable difference of opinion as to normal and abnormal glands. In general the factories' "limit of normal" corresponds to the group of moderate glandular hyperplasia and generally the markedly enlarged glands are not used. The commercial preparations then contain a mixture of normal and abnormal glands and

may explain in part at least the great variation in activity clinically, and especially its generally injurious effects in the group of glandular hyperplasias in man and animals.

It is my belief that these hyperplased glands have a hypersecretion quantitatively, but that it is greatly altered, and is deficient in some important physiological constituent, and also has a highly toxic action.

(2) *Relation of the glandular hyperplasias to the thyroid in toxic (exophthalmic) goitre.*—There are some good reasons for believing that the disease in dogs, sheep, and cattle, characterized by hyperplasia of the thyroid with enlargement of the spleen; thymus and lymph glands are very closely related to toxic (exophthalmic) goitre in man.

For, aside from the occasional lesions found in the restiform body, medulla and cervical sympathetic, there are well refined and quite constant lesions, the most characteristic of which are glandular hyperplasia of the thyroid, persistence of the thymus as pointed out by Mackenzie (21), with enlargement of the spleen and lymph glands, thus bringing the lesions observed in animals to resemble very closely the lesions found in Graves' disease.

As pointed out before there is every reason to believe that these hyperplased glands have a hypersecretion quantitatively, but that physiologically it is deficient in some important constituent, and that this quantitative excess has a toxic action. The same conditions are observed in Graves' disease.

The belief has been expressed that these changes occurring in dog and sheep are to be considered cretinoid in nature, and it is my belief that further work will show a still closer relation between the glandular hyperplasias in animals and toxic (exophthalmic) goitre in man than I have indicated and that we shall recognize these changes as stages in the course toward myxœdema or cretinism. It is interesting to note that Ord (22), in 1898, wrote: "It appears to me probable that we shall recognize in the near future, more and more the occurrence of a stage of hypertrophy of the thyroid gland with or without the signs of Graves' disease as an antecedent of myxœdema." Howard (23) also has recently brought forward this idea with emphasis, and adds: "I believe that a history of exophthalmic goitre preceding the onset of myxœdema would be more frequently elicited if more careful inquiry were made." It might be pointed out here that myxœdema, according to case reports, rarely precedes, occasionally accompanies, and frequently follows the symptom-complex of Graves' disease.

This special phase of the subject is exceedingly important and no doubt it has been lost sight of largely through the hypersecretion theory of Gauthier (24), and Moebius (25). I am also inclined to think that the more we study toxic (exophthalmic) goitre, the more closely we shall find it related to the cretinoid condition of dog, sheep, and cattle; also that it is a reaction to a deficiency (29), and if the deficiency is met the gland reverts to a colloid type, and if not, the organism exhausts itself in the attempt to meet the deficiency but, to again quote Ord (26), "Such proliferation ending in the replacement of the true glandular structure by a fibrous material and consequent destruction of the function of the gland." Thus there is reason for believing that toxic (exophthalmic) goitre is a reaction to a deficiency and represents one step toward myxœdema, in which the true changes are masked by the toxic manifestations of an excessive secretion of toxic substance.

(3) *Relation of the glandular hyperplasias to ether anæsthesia.*—In the course of surgical work with dogs one can clearly notice distinct differences in the effect of ether on those with and without goitre. This was brought forcibly to me after the loss of some cretin dogs by attempting ether anæsthesia. On inquiring into the matter I found that it was common knowledge about the laboratory. The janitor was aware of the danger of sudden death and avoided goitrous dogs for use in the physiological department. In Dr. Crile's work great differences in resistance were noticeable and as I examined all the thyroids in routine, I could sort out those dogs with excellent resistance by their more normal thyroids.

Dr. D. H. Dolley, in his large experience with dogs in Crile's laboratory also noticed great variations in their resistance to ether and he told me that he avoided using goitrous dogs when possible.

That there are great variations in the resistance of dogs to ether is clear and it occurs for the most part in those with hyperplasia of the thyroid and enlargement of the lymphoid tissues.

The question arises: Have these changes any causal relation to the phenomena of lowered resistance and sudden death? I think there is a definite relationship for the following reasons:

(1) It is limited to those dogs and sheep which have goitre and general prominence of the lymphoid tissues.

(2) Administration of iodine will relieve the danger.

(3) Toxic (exophthalmic) goitre in man, having practically the same anatomical changes, show the same phenomena of lowered resistance and danger of sudden death under ether anæsthesia. Extensive data are not yet in hand, but an hypothesis based on our observations thus far may not be misleading. That is these subjects may be suffering from an exhaustion which particularly manifests itself in the central nervous system, and that this exhaustion with its consequent dangers is comparable to that occurring in severe anæmias; in the one case there is an iodine deficiency, in the other it is iron.

(4) *Effect of iodine on the human thyroid.*—I have but one observation namely: That of 173 human autopsy specimens examined, all of those cases which had had iodine administered just prior to death showed the acinar epithelium to be in the quiescent (low cubical) stage.

Complications in the Dogs' Thyroid.

They are rare. Hæmorrhagic-cystic (28) changes are the usual ones. They generally occur during the stage of glandular hyperplasia. They seem to depend on an insufficient stroma reaction to support the great increase in the blood-supply and epithelial elements with consequent rupture of the smaller vessels. In colloid goitres, calcification, though very rare, is the most common, and usually occurs in the walls of the arteries and the capsule of the gland.

Conclusions.

(1) That iodine is essential for normal thyroid activity.

(2) That glandular hyperplasia is a physiological reaction to a deficiency, and it is to be considered cretinoid in nature.

(3) That colloid goitre is usually preceded by a stage of glandular hyperplasia, and in its uncomplicated form is the quiescent stage of the same.

(4) That the associated enlargement of the spleen, thymus and lymph glands, in varying degrees, is an integral part of the affection.

(5) That the dangers associated with ether anæsthesia in dogs are similar to those observed in toxic (exophthalmic) goitre and lymphatism in man.

(6) That the commercial desiccated thyroid contains a mixture of normal and abnormal thyroids, and that this explains a part of its varied action clinically.

(7) That further observations will show a closer relationship between the glandular hyperplasias in animals and toxic (exophthalmic) goitre in man than has been indicated.

I wish to thank Dr. R. G. Perkins for help with the microphotographs, and also Drs. M. B. Bonta and C. H. Lenhart for their unstinted services in the operative work.

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Notes on the Microphotographs.

The sections were taken from the routine files and represent types and moderate degrees of the changes. All sections are formalin (four per cent), celloidin-hæmatoxylin, and eosin preparations unless otherwise indicated. The magnification is the same in all. Leitz, oc. 4, obj. 3, × 95 diameters.

(1) Normal human thyroid (Zenker spec.).

(2) Primary toxic (exophthalmic) goitre, human (Zenker spec.).

(3) Colloid goitre, human.

(4) Normal thyroid, dog.

(5) Moderate glandular hyperplasia, dog.

(6) Early stage of colloid goitre, dog (reversion of early stage of glandular hyperplasia). Note the remnants of intra-acinar projections; also compare with the normal.

(7) Normal thyroid, sheep.

(8) Moderate grandular hyperplasia, sheep.

(9) Colloid goitre, sheep.

(10) Normal thyroid, ox.

(11) Moderate glandular hyperplasia, ox.

(12) Marked glandular hyperplasia, ox.

(13) Moderate glandular hyperplasia, dog. (Specimen removed before the administration of iodine.)

(14) Same gland as No. 13. (Specimen removed during the administration of iodine.)

(15) Same gland as No. 13. (Specimen removed after the administration of iodine.)

(16) Composite picture showing moderate glandular hyperplasia of right lobe, and reverted (colloid) stage of left lobe. The left lobe was removed four weeks after the right, and iodine was administered in the interval.

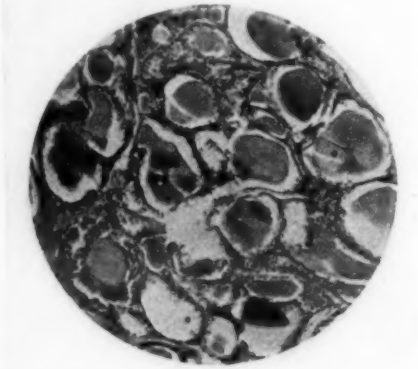


FIG. 1.

FIG. 2.

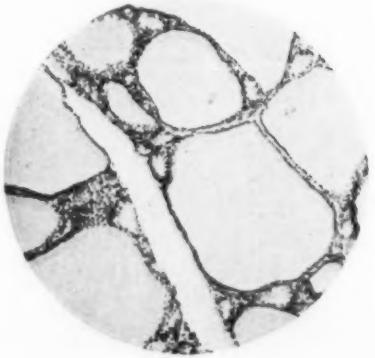


FIG. 3.

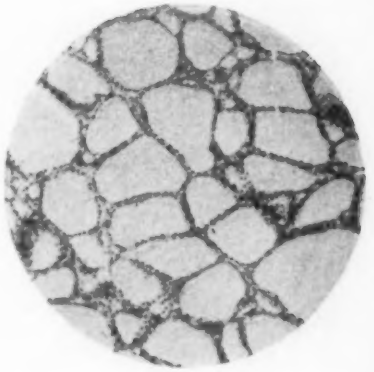


FIG. 4.

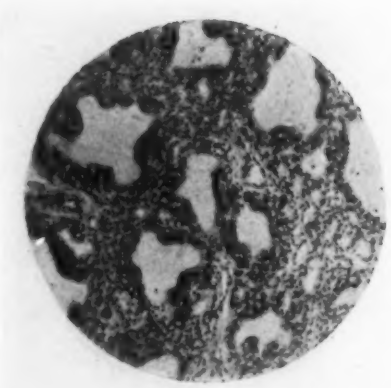
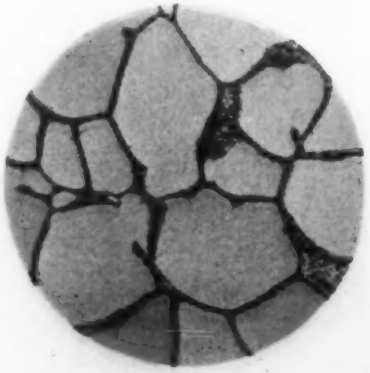


FIG. 5.



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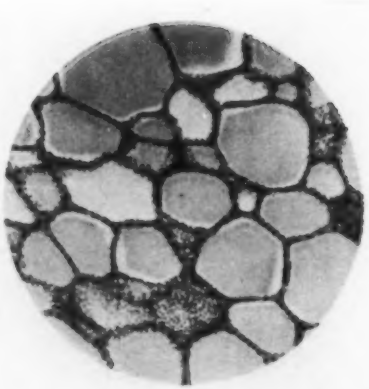

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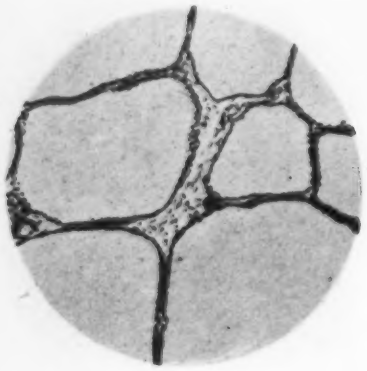

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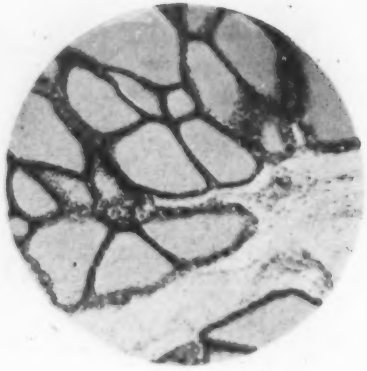


FIG. 10.

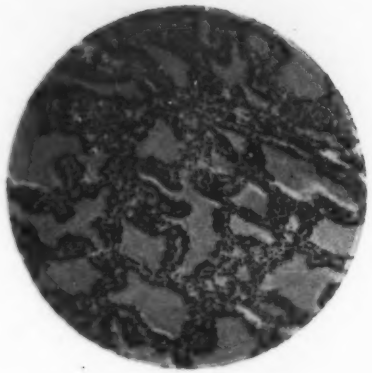


FIG. 11.

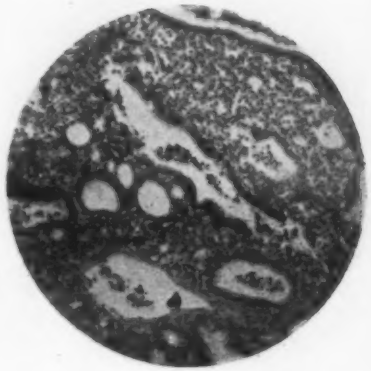


FIG. 12.

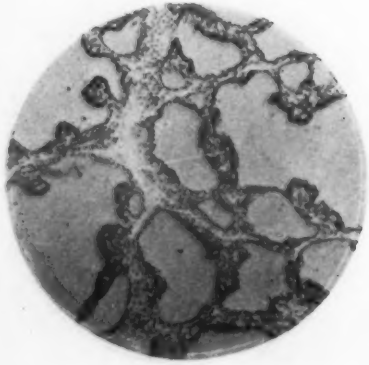
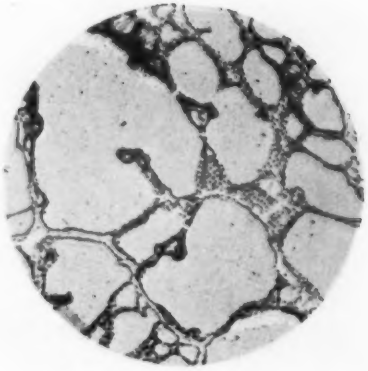


FIG. 13.



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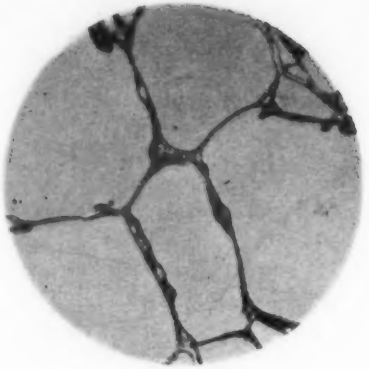

FIG. 15.

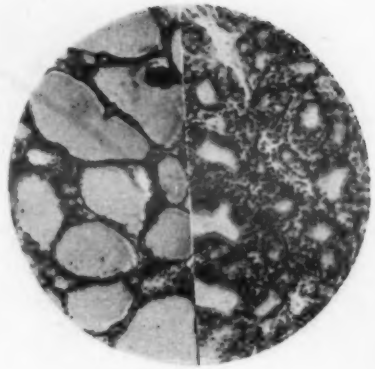

FIG. 16.

EXPERIMENTAL EPITHELIAL PROLIFERATIONS OF SKIN AND MUCOUS MEMBRANES.

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The work of Fischer has opened up an entirely new line of experimentation regarding the development of tumors, and it was with the idea of repeating his experiments and carrying the work a little farther that this work was undertaken. The very first experiment proved quite conclusively (Fig. 1), that epithelial proliferation of the skin could be readily produced by the injection of a solution, Sudan III, in oil, and sections were obtained that resembled epithelioma of the skin in no slight degree. The negative results of Fischer in the breast, stomach, and intestines were at first substantiated by the results obtained in several operations and injections in the stomach. The abruptness with which the connective tissue changes stopped at the muscularis mucosa made it seem that perhaps the technique was at fault and the oil had no chance to act on the epithelium; so the experiments were repeated on the rectum, where the injections could be made as frequently as necessary, and the oil more readily inserted into the mucosa. The mucous membrane of the mouth also proved to be a very fertile field for experimentation.

In the following paragraphs, the various experiments performed will be briefly given.

The work on the skin was performed on the rabbit, guinea-pig, and chicken. The experiments on the rabbit's ear covered the greater part of the work. The first one was the repetition of Fischer's experiment, and as the photo-micrographs are given in the text, the details will be briefly indicated.

EXP. Ia.—Large black rabbit.

January 16, 1907, 11 a. m. Injected Sudan III oil into the middle of the lateral margin of both ears.

January 18 and 22. Repeated the injection. The left ear is only slightly thickened and the skin shows slight, if any, excoriation. The right is greatly thickened and excoriated over its entire surface; it is about three times its normal thickness.

January 28. Pieces removed from both ears.

February 1. Animal died. Blocks taken from both ears. Autopsy showed nothing of note except that glands at the base of ears are large, swollen, and distended with oil. Considerable oil in capillaries of lungs.

In the gross, the excised portions had very much the appearance of the cut section of a carcinoma of the skin, small finger like processes of a slightly more opaque white color could be seen extending down into the fibrous tissue. This was even better brought out after the piece had been hardened in alcohol and all the Sudan oil dissolved out.

Microscopically, the section is one of the most interesting of the series (Fig. 2). The injected side of the ear is about three times the size of the inner which has been only affected by the oil that has passed through the fenestra in the cartilage. The surface epithelium is greatly thickened, which is due in part to an increase in cells and in part to small vesicles which contain serum and a few pus cells. The cells of the epidermis, although they are rapidly proliferating as shown by numerous mitotic figures, do not extend any great distance downward into the fibrous tissue. The greater part of the epithelial proliferation comes from the hair follicles and sebaceous glands which have grown to such a degree that they cannot be distinguished, only the large concentrically arranged epithelial masses of chitinous material indicating the original follicles. Contrary to the assertion of Jores, it seems quite evident that the most marked downward growth is from the lower portions of the hair follicles; connections can be traced from them down almost to the cartilage. At the level of the hair follicles, the masses of epithelium take up the greater part of the surface, but lower down the ear consists of a mass of young fibrous tissue in which lie very numerous small masses of epithelium in bizarre shapes, and when growing around oil droplets, they form a thin lining of slender cells that are drawn out like fibroblasts. In the large masses there is considerable central epithelial degneration, resembling somewhat the pearls of carcinoma. The mitoses are very frequent, but contrary to Fischer's findings, are nearly all regular.

On the opposite side of the cartilage, the picture is that of the reaction when the irritant is less intense, showing merely the thickening of the epidermis, and the rapid proliferation of the cells of the hair follicles and glands, without any marked downgrowth of epithelium into the deeper tissues.

The sections taken on the 16th day are of interest because they show the very rapid degeneration of the epithelium. Almost the entire mass of cells excepting perhaps the outside layer in contact with the stroma show marked degenerative changes; the nuclei are dark and shrunken, the cell outlines indistinct and the protoplasm filled with bluish grandular material. Mitotic figures are absent.

The other six experiments with Sudan III, and Scharlach R oil gave practically the same results except that the epithelium did not show quite so much splitting up into small masses. One of the experiments showed very beautifully the invasion of the cartilage by the epithelium; as already previously described by Fischer. The perichondrium and a small portion of the cartilage has been destroyed and a number of cartilage cells have become necrotic.

In the course of his discussion, Fischer makes the statement that if the chemotatic action of the oil could be made a continuous one, the growth of the tumor would be constant and malignant. Working along this line, two rabbits were injected once a week for a period covering two months.

The reaction was very nearly the same in both animals, the ears gradually increased in size, became very firm and elastic, and the surface formed at first thick scales and later cast off large masses of white epithelial debris. At this stage, the

injections became very difficult to make because of the large epithelial pearls that rapidly ruptured as soon as the oil was forced into them. Portions of the ear were removed 34 days in one and 52 days in the other after the first injection of Sudan III oil. In the gross, the one specimen was a greatly thickened ear tip measuring 5-6 mm. across in its widest portion; as the two were practically identical as far as the epithelial changes go, the one in which a chondroma was produced will be briefly described. The surface was quite rough and irregular, and with the finger, several large white masses which projected above the surface could be shelled out. The same structures were found deeper down in the fibrous tissue on the cut section and could be readily expressed on pressure. The fibrous tissue contained considerable pigmented oil, but none was seen in the epithelial spaces.

Microscopically, the thickening is seen to be due to great proliferation of fibrous tissue which, especially in its outer portion where it comes in contact with the epithelium is of a very loose texture, being formed almost entirely of spindle cells. In its central portion, there are numerous, good sized vacuoles, some without a lining which no doubt in the fresh state contained oil, and others filled up with a rather irregular mass of cells, the outlines of which are indistinct; their nuclei, however, are large and vesicular.

The most marked feature of the epithelial proliferation are the large cysts lined by a thick layer of proliferating epithelium, in which a small number of mitotic figures can be found. Some of the cysts open on the surface, others are deeper down and completely surrounded by fibrous tissue. The surface epithelium is for the most part a thin layer of cells that sends occasional processes into the loose tissue beneath. At one end of the section between two diverging plates of cartilage there is a multiple chondroma developing in the loose fibrous tissue. These plates show some lateral outgrowth of cartilage. The areas of cartilage vary from masses about 1 mm. in diameter to minute ones consisting of only four or five cells. These cartilage cells can be seen in all transition stages from connective tissue cells.

The organs at autopsy showed nothing of note except the marked sclerosis of the gland draining the ear. Nothing comparable to the proliferation of the alveolar epithelium as described by Fischer could be demonstrated in numerous sections of the lungs.

To determine what part, if any, the oil played in the process, various other solvents were substituted for the oil. Paraffin (melting pt. 45°) was tried, but it was found that although the epithelial changes were produced to a slight degree, the material had a great tendency to collect in such large masses that it produced necroses. A mixture of oil and paraffin was next tried with better success, and although the combination does not produce the pretty results that the oil alone does in the skin, it was found to be of great value in the experiments in the mucous membranes, where oil alone is too rapidly absorbed.

The specimens produced by Sudan oil-paraffin showed a great tendency on the part of the fibrous tissue to form large conglomerate masses of giant cells. The epithelium in 15 days had grown quite diffusely down into the newly formed tissue, on a small scale to be compared with Fig. 1.

Sudan III dissolved in ether, xylol, and dilute alcohol all produced such acute irritation that they led to necrosis on repeated injections.

Two experiments tried with osmic acid oil, and two with dimethylamidoazo-benzol (the latter a product related to Sudan III, but of basic instead of acid properties) were negative. There was some thickening of the epithelium and even some proliferation of the cells of the hair follicles in a 19-day dimethylamidoazo-benzol specimen. The osmic acid experiments were very nearly the same. A specimen obtained after 4 injections covering a period of 17 days, showed some slight thickening, and in several small areas a hyperplasia of the hair follicle cells but not to be compared with a Sudan specimen of the same age.

The four experiments on guinea-pigs with Sudan oil and Sudan oil-paraffin gave the same results as in the rabbit. A 15-day specimen of the oil injection shows a very marked thickening of the surface epithelium and in the lower layers, numerous mitotic figures can be seen, especially in those areas where epithelial processes are extending down into the very cellular fibrous tissue. The hair follicles also show very marked increase in size and from their lower portions numerous processes extend out irregularly into the inflammatory tissue. The addition of paraffin changes the microscopic picture considerably. The reaction is more local, the side opposite is not affected at all and the injected side only a very short distance laterally. The ear is considerably thicker than the other, due principally to a great increase in fibrous tissue in which foreign body giant cells are a very marked feature. The epithelium is markedly thickened and has grown completely around the great mass of oil-paraffin. From its under surface, small epithelial buds extend into the fibrous tissue. To the side of this central mass, the proliferation of the hair follicles is quite marked. Mitotic figures are very frequent.

The only other animal that the injection of Sudan oil was tried on was the chicken. The comb and the skin under the wing were injected, the latter with oil-paraffin. The results were negative; there was produced a considerable thickening of the epithelium but no downgrowth in either place. That the oil came in direct contact with the epithelium is shown by the formation of young connective tissue just beneath the epidermis.

Having determined that the Sudan oil acts with great constancy in producing epithelial proliferations of the skin, its effect was next tried on the various mucous membranes of the rabbit. The lining of the bladder, œsophagus, stomach, rectum, and mouth were injected with a mixture of oil and paraffin in the majority of cases.

1. *Bladder.*—A laparotomy was performed and the Sudan oil-paraffin injected by inserting the needle through the serosa of the bladder. Two rabbits were injected; one was sacrificed 12 days after the operation and the other after 22 days. In the second, a small area was injected with dimethylamidoazo-

benzol oil. Microscopically, the bladder on opening presented a large papilloma distended with oil. On microscopical examination, there was found a great growth of fibrous tissue just under the epithelium but no proliferation whatever of this tissue. The same condition was found in the dimethylamidoazo-benzol injections.

2. *Œsophagus.*—An incision was made into the neck of the rabbit, the œsophagus was dissected out, and injected with oil at one point, and 2 cm. lower down with oil-paraffin. The animal was sacrificed 12 days later. The findings consisted of a marked proliferation of fibrous tissue, rich in giant cells in the submucosa. Epithelial changes were entirely absent.

3. *Stomach.*—The two attempts to produce proliferation of the gastric mucosa failed. The abdominal cavity was opened, the muscle coats cut through and the Sudan oil-paraffin injected directly into the submucosa. In each case, there was a marked fibrous tissue reaction in the submucosa which extended as far inward as the muscularis mucosa and then ended abruptly, the mucosa being perfectly normal.

4. *Mouth.*—The relation of the epithelium of the mouth and skin is so close that it was almost to be expected that the epithelium of the former would react to Sudan III like the latter, and so it proved to be. Six experiments were performed, three with Sudan oil and three with Scharlach R oil-paraffin.

Exp. IIa.—White and gray rabbit.
February 4, 1907. Injected Soudan III oil into right cheek.
February 11. Repeated injection.
February 15. Repeated injection.
February 18. Repeated injection.
February 21. Excised injected portion of cheek under ether. The section shown in Fig. 3 was taken from this block and shows very well the character of the epithelial downgrowth, a slender process that spreads out and grows around the mass of pus cells that have collected in the oil droplets. The mitoses are very numerous.

In another section, removed six days after a single injection with Scharlach R oil-paraffin, only thickening of the surface epithelium and numerous mitotic figures in the basal layer of cells are to be made out.

The most diffuse growth of epithelium in the tissue was obtained in Exp. II*f* after three injections of Scharlach R oil-paraffin in the cheek. The section is shown in Fig. 4. The epithelium is growing in great masses diffusely in the tissues, surrounding masses of purulent exudate, and extending out in thin streaks to oil drops further along, surrounding them and penetrating still further into the new formed fibrous tissue. This same rabbit had five injections of Sudan oil-paraffin into another portion of the mucous membrane, and was finally sacrificed on the 34th day after the first injection. In the gross, the downgrowth of epithelium could be made out as several grayish lines extending in from the surface; although the epithelium is in larger masses, it does not show nearly the diffuseness of growth of Fig. 4. Throughout the infiltrated portion, there are numerous polymorphonuclear leucocytes. In these large epithelial masses, the preservation of the cells is much better than in those of the same size in the skin.

5. *Rectum.*—The failure of the experiments in the stomach and œsophagus seemed to be attributable to the presence of the muscularis mucosa which prevented the necessary direct action of the oil on the epithelium. To overcome this obstacle and also to make more frequent injections possible, the rectum was selected to work on. The technique employed was simple. The rectum was stripped back until a large portion of mucosa was visible. The needle was then introduced, either through the mucosa, or inserted in the skin just beyond and carried out under the mucosa. Multiple injections were made each time, as it was very difficult to get the oil in just beneath the mucosa. The first two experiments were negative. In the first, three injections of Sudan oil were made, the animal dying on the 12th day, and in the second, the animal died on the 22d day after three injections. Except for slight fibrous tissue changes in the submucosa, there was no difference from the normal. The third experiment because of its importance will be reported in detail.

Exp. VIII*b*. Large gray and white female rabbit.
February 28, 1907. Injected Scharlach R oil-paraffin under rectal mucosa.
March 5. Repeated injection—small amount.
March 7. Repeated injection—small amount multiple.
March 12. Repeated injection.
April 4. Repeated injection.
April 23. Repeated injection.
April 30. Repeated injection—large amount retained.
May 9. Repeated injection—large amount retained.
May 14. Repeated injection.
May 17. Animal died without any apparent cause.

The organs were found practically normal.

Gross description of the rectum: On opening the rectum a considerable amount of oil oozed from the section. The submucosa was greatly thickened by fibrous tissue and oil droplets. At one point, just inside the line of juncture of skin and mucous membrane, there is a small white nodule lying just below the mucosa. Making several other longitudinal cuts, two other areas of similar nature are found. In the one, there are several grayish white lines extending for some distance down into the submucosa; in the other, there is a larger grayish mass lying in the submucosa. A diagnosis of probable downgrowth of epithelium was made.

Microscopically, this diagnosis was verified. There has been produced multiple downgrowth of cylindrical epithelium into the submucosa. In two of the sections, the connection with the mucosa cannot be made out. The alveoli are more or less normal, although in both there is one large irregular lined space. In both, there is some increase of fibrous tissue in the mucosa and numerous vacuoles formed by oil droplets, but no definite metaplasia of the epithelium.

The third section from which Fig. 1 is taken is markedly different; the proliferation is more irregular and there has been a metaplasia of cylindrical to squamous with a return to

the cylindrical type in some of the alveoli further down in the tissue. The section was cut parallel to the rectum so that there is no possibility that the squamous epithelium, found, as it is, with the cylindrical epithelium on both sides of it, got there by the obliquity of the cut. In the part from which the downgrowth has taken place the epithelium shows great thickening, the single row of cylindrical cells shades over into a layer of squamous epithelium varying from five to ten cells in thickness; at the base of several of the processes, the cells on the surface return to the cylindrical form. The squamous epithelium above narrows down to a several cell layer and gradually changes back to the cylindrical type. The epithelium rests on a newly formed connective tissue rich in plasma cells and containing some eosinophiles and oil vacuoles.

The muscularis mucosa has been broken through and pushed to the side by the large epithelial masses.

Beneath the muscularis mucosa, the other main solid epithelial mass of squamous epithelium opens up into a large space partly filled with detritus and lined by many layers of squamous epithelium which on the surface has a marked tendency to return to the cylindrical type. Extending out from this alveolus, are numerous small solid processes which in cross section show a tendency to the formation of alveoli, and the lining cells a return to their original form. A single alveolus lined by three layers of cells, the inner most one of which is cylindrical, is found down in the inner muscular coat; its connection with the main mass of epithelium could not be made out in any of the sections. At one other point just beneath the muscularis mucosa there is an alveolus filled with detritus in which are seen numerous leucocytes and lined by a single layer of cuboidal cells. Some mitoses are found but only infrequently.

The positive results obtained in this last experiment make it seem probable that with improved technique, the same sort of changes can be produced in stomach and œsophagus.

The experiments show quite conclusively that the effect of Sudan III and Scharlach R is a general one, that they act on different sorts of epithelium as well as on the different connective tissue elements including cartilage.

The fact that he could obtain proliferation only of the skin has led Fischer to suppose that Sudan III and Scharlach R had some definite chemical affinity for the surface epithelium. That there is some interaction cannot be doubted after examining Fischer's illustration, but that this action is in any way specific, the above given experiments controvert quite definitely and no doubt, if the experiment that was performed in the rectum were repeated in the stomach, intestines, and œsophagus, identical results would be obtained so that the action of the Sudan III can hardly be thought of as a specific attraxin, but rather something that by interaction with the connective tissue produces a soil that is ready for epithelial development. The development of cartilage from fibrous tissue seems more evidence to show how marked is the effect of the Sudan oil on the connective tissue.

In the skin experiments, Jores reports most of the epithelial growth from the hair follicles at the entrance of the sebaceous glands, and thinks that failure on mucous membrane may easily be due to absence of hair follicles. In cases where the reaction is very mild it does seem as though most of the effect manifested itself in the upper portion of the hair follicles but whenever any more active proliferation occurs, the skin and especially the lower portions of the hair follicles respond to the attraxin. As regards mucous membranes, the numerous positive results in mouth and rectum indicate the relative importance that the hair follicles play. The work of Snow is rather difficult to explain; how he could have obtained such a series of absolutely negative experiments is hard to see when in practically every experiment on the skin more or less marked proliferations of the skin were obtained. His conclusions are hardly justifiable, especially as it is almost inconceivable that Fischer's results and drawing could be due to any obliquity of the section. The work of McConnell, Jores, and that just described, all confirm the essentials of Fischer's work.

The experiments on the rectum are perhaps of more interest than any of the others. It proves that very close contact must take place between epithelium and oil in order that any reaction take place; and it explains the negative results obtained in the stomach and œsophagus, though not of the bladder. It further shows that cylindrical epithelium remains so, only so long as it lines a lumen, and as soon as it grows in masses it conforms to the squamous type; and just as readily returns to the cylindrical type when lumina form in the epithelial masses. The same thing occurs in the intestinal tube during embryonic development. The canal becomes obliterated by an excessive proliferation of epithelium which is of the squamous type, and as soon as small lumina again appear the cells about them return to their cylindrical form. This metaplasia, though of great interest, shows how different the process is from carcinoma in which the character of the cells remains constant.

The relation of these experiments to the cancer problem has been dealt with at great length by Fischer, who has set up an entirely new theory to explain the growth of malignant tumors. The quite uniform action of Sudan on the different epithelia makes it seem that it is rather a common reaction on the part of epithelium than a specific attraxin that produces the very interesting proliferations. The importance of Fischer's work is quite manifest, and will lead without doubt to many interesting and useful results.

In conclusion, I desire to thank Dr. Welch for his kind suggestions and the interest that he took in this work.

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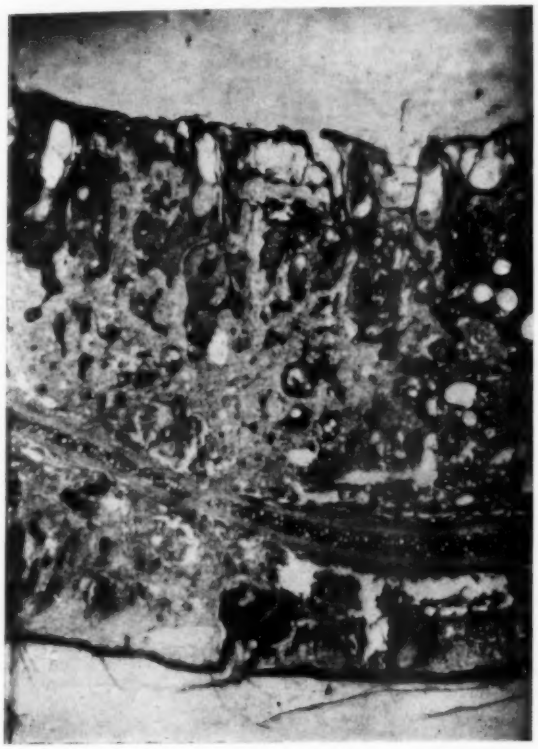

FIG. 1.—Experiment Ia. Showing gross relations of epithelial processes growing down into tissue of ear. 12-day specimen.

FIG. 3.—Experiment IIa. Mucous membrane of mouth. 17-day specimen.

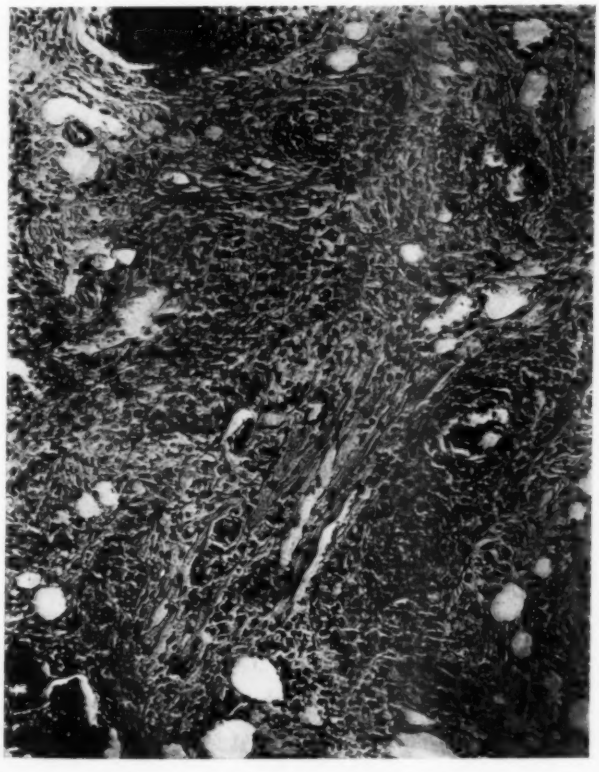

FIG. 4.—Experiment IIb. Mucous membrane of mouth. Growth of epithelium deep in tissues.

FIG. 5.—Experiment VIIIb. Rectum. Metaplasia and downgrowth of cylindrical epithelium.

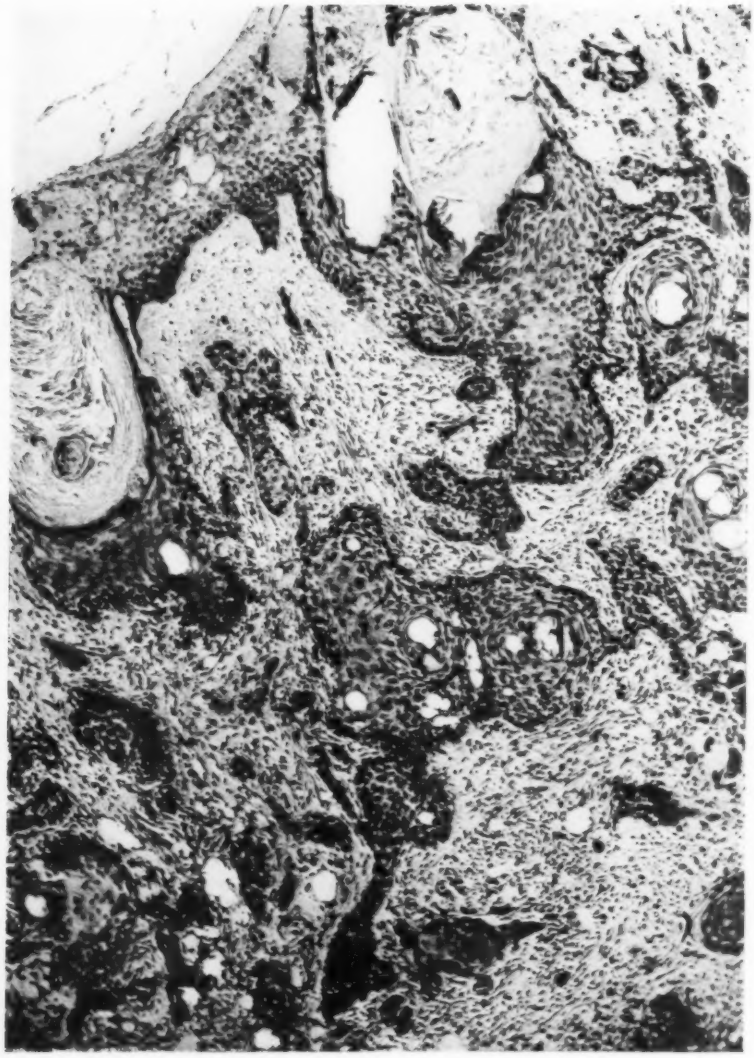

FIG. 2.—Experiment Ia. Showing proliferation of epithelium of rabbit's ear in detail. 12-day specimen.

AN EXPERIMENTAL MULTIPLE CHONDROMA.

By HENRY F. HELMHOLZ, M. D.,
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In the course of experimentation in rabbits to determine what effect the oft-repeated and long-continued injections of Sudan III oil would have on the epithelium of the rabbit's ear, there was found on microscopic examination of a block of tissue, removed a little over two months after the first injection, a multiple chondroma. At the time only a small portion of the ear was removed and the injections continued. The animal died suddenly a month and a half later, and when picked up in the morning it was noticed that the injected ear had been entirely eaten away, and the further development of the tumor unfortunately lost. The length of time necessary for the experiment prevented a repetition of the same. Another animal that had been injected for a period of about one month and a half showed no cartilaginous changes. In several others, however, of somewhat shorter duration, small outgrowths from the sides of the cartilage plates were noted, but in none, were any distinct masses of cartilage lying free in fibrous tissue.

The technique employed in the experiment is in brief as follows. A solution of Sudan III (Grübler) in olive oil, containing an excess of the pigment was prepared and sterilized and, while still hot, injected with a sterile hypodermic needle as near as possible into the tissue just beneath the epidermis. From five to ten minims were injected, but rarely more than half of that amount remained within the tissue. While making the injection the ear was clamped just below the point at which the needle was inserted so that as little as possible of the oil passed immediately into the circulation. This may account for the long life of the rabbit.

The following is a brief outline of the experiment:

Exp. Ie.—Large white rabbit, female.

January 31, 1907. Sudan III oil injected into both ear tips.

February 4. Tip of left ear removed. Right slightly swollen.

February 11. Right ear re-injected. Ear greatly swollen, tender and scaly.

February 13. Right ear re-injected. Ear greatly swollen, tender and scaly.

February 18. Right ear re-injected, only small amount of oil retained.

February 21. Right ear re-injected, ear markedly swollen, thick scales on, in, and outside of ear. Swelling limited entirely to tip.

February 28. Right ear re-injected. Swelling has subsided to some extent. Ear thick and elastic.

March 8. Right ear re-injected. Rather difficult to inject oil because of numerous large spaces filled with epithelial debris which quickly ruptures when the oil is forced into them.

March 14. Right ear re-injected. Numerous large degenerated epithelial masses can be scraped out of the surface.

March 20. Right ear re-injected.

March 27. Right ear re-injected.

April 4. Removed small portion of ear tip.

The tip of the ear measured 6 mm. in thickness on cross section. Its surface was rough and irregular, from the depressions small masses of putty-like material could be scraped. The cut section showed an ear thickened out of all proportion by an increase in fibrous tissue, in which numerous large epithelial alveoli filled with debris could be seen; this material was readily squeezed out. In the fresh state there was considerable oil in the stroma, but none in the epithelial masses. No evidence of cartilaginous proliferation was made out in the gross.

On microscopic examination there was found at one end of the section a mass of very loose fibrous tissue, in which numerous large and smaller islands of cartilage were developing. A single cartilage plate extended almost the entire length of the section. Just before reaching this area it divided into two plates which diverged at an angle of about 45°.

It might be supposed that the cartilage plate had here been torn apart, but comparing the position of the plates in a number of sections and the presence of a V-shaped mass of cartilage at the apex of the triangle, made it certain that there were normally two plates of cartilage. Along their surfaces there were numerous small knob-like thickenings, consisting of young cartilage cells. The angle formed by these two sheets of cartilage was filled in with a loose newly formed fibrous tissue, containing numerous large vacuoles, which no doubt in the fresh state were filled with oil. In the inner portion of the angle the fibrous tissue is somewhat denser and more vascular, and showed several alveoli filled with proliferating endothelium. Farther out the predominent cell is a small stellate one, bound together by a thin network of fibrils; in areas these cells become grouped together in bundles. The large vacuoles, made by the oil were in part lined directly by the masses of cartilage, in one instance completely as seen in Fig. 1. It is in this loose tissue that the numerous masses of cartilage were found. The connective tissue shaded off so gradually into the cartilage, that at many points it was difficult to determine where one began, and the other left off. This was especially true of several of the more centrally lying masses that were not surrounded by perichondrium, in which the connective tissue cells could be seen in all transitions to cartilage. Fig. 2 shows the condition extremely well. The cartilage, as seen in Fig. 1, was present in large masses which stained typically blue, and in small areas, some of which consisted of only three or four cells. In the latter the cartilage cells could be seen lying free in a uniform pink staining hyaline mass, in which occasionally fibres could still be made out. In several of the larger areas of cartilage the cells had undergone necrosis, and the cell spaces were filled with blue granular detritus, in others as many as five cells could be found in a single lacuna; in still other areas, especially the younger ones, multinucleated cells were found, but in no instance were any karyokinetic figures definitely made out, although many structures were seen that resembled them.

In these same small masses the cells have undergone vacuolar degeneration, and what was more remarkable the nuclei of many have increased so in size that they fill practically the entire lacuna.

The areas of especial interest were those in which the cells were in transition stages to cartilage. The connective tissue cells seemed to draw in their processes, and their outline became very distinct, and their nuclei became larger and more vesicular. The interstitial substance lost its fibrillar character, and stained lighter and more uniformally pink, and the cell body, which at first was still directly in contact with it, retracted and was seen to lie free in its lacuna. So that just before the cell retracted it is impossible to say whether it was a fibroblast or a cartilage cell that one was dealing with.

This experiment showed that Sudan III, besides its decided effect on epithelium also exerted a powerful stimulating influence upon the cartilage producing tissues. The direct proliferation of the cartilage cells was seen by the thickening of the primary cartilaginous plates; the growth of the independent islands of cartilage, however, could not be so explained. The direct transitions from connective tissue to cartilage showed that in great part the masses were produced by metaplasia. Two explanations are possible: (1) That the perichondrium of the normal plates has undergone enormous hyperplasia, and, in its rapid growth has produced a tissue of very loose fibrillar type which is again slowly assuming its cartilage forming function; or (2) That the connective tissue by the stimulation of the Sudan III has returned to the type of embryonic mesoblastic cell, with the power of forming any of the connective tissue elements. It might be supposed that the original cartilage plate had been broken into small fragments by the pressure of the injections, but that seems rather improbable, and would not explain the metaplasia.

Of the two theories proposed it seems that the first has the most in its favor. The Sudan oil has produced a marked proliferation of perichondrial cells, just as it acts on the other connective tissue cells. This growth has been so rapid that for the most part the cells have retained their embryonic form of stellate cells, and only later as they slowly ripen begun to change into cartilage cells and these in turn gone on proliferating to form the large masses, as seen in Fig. 1. It seems more rational to think of the process rather as an excessive stimulation of perichondrial cells, than the taking on of a new function by the ordinary connective tissue cell. Microscopically, the stellate cells that were developing cartilage cannot be distinguished from another connective tissue cell of the same type.

The bearing that this experiment has on the views of Fischer regarding the specificity of action of Sudan III, might be dwelt on for a moment. In his article he described the action of Sudan III as specific for the epithelium of the skin; that a definite attraxin produced the proliferations; that attraxin is not specific for squamous epithelium was shown in another place (2), and this experiment shows that a specific connective tissue element cartilage responds to the same attraxin, so that if the action is to be considered as due to an attraxin, its nature and action must be far more general than Fischer described.

At this point I wish to thank Dr. Welch for the kind interest he has taken in this work.

As far as can be determined from the catalogue of the Surgeon-General Library and the Index Medicus this is the first time that a chondroma has been experimentally produced.

TWO CASES OF ATRESIA OF THE SMALL INTESTINE.

I. MULTIPLE CONGENITAL ATRESIA OF THE JEJUNUM.
II. VALVULAR ATRESIA AND SECONDARY INFLAMMATORY OBSTRUCTION OF JEJUNUM.

By Henry F. Helmholz, M. D.,
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Atresia of the small intestine is a condition that is still very unsatisfactorily explained in the great majority of reported cases. One thing which has been quite consistently neglected is the histological examination of the specimens. How this may affect the etiology is best illustrated by Case III of Chiari's series in which, on macroscopic examination, he came to the conclusion that the occlusion was due to axial twisting of the mesentery, but after making microscopic preparations, he discovered an intussusceptum in the distal loop, and so decided that the primary cause was the intussusception. The two cases named in the title become of especial interest when viewed in the light of the histological findings. The cases in detail are as follows:

Case I.—Baby S. Aet. 2 days. Died October 21, 1906.

Clinical History.—Family history was negative. Child was born in cab on way to hospital. On arriving in ward child cried and breathed well, its head and arms were markedly cyanotic. It was a typical blue baby, a systolic murmur was heard loudest over sternum and present also over entire chest. The child did not vomit. It was given hot water and brandy in small amounts and strychnia. Its weight at birth was 2755 gm., on the second day, 2568 gm. Temperature, 95°. Death occurred on second day. The autopsy, 2800 of the Johns Hopkins Hospital series, showed the following conditions:

Anatomical diagnosis.—Malformation of heart; congestion of viscera and subcutaneous tissue; multiple congenital atresia of intestine; broncho-pneumonia; uric acid infarcts of kidney; cirrhosis of liver; chronic fibrous peritonitis; cirrhosis of pancreas; anomalous mesenteric circulation.

Body was that of a white male child of good development; 50 cm. in length. Rigor mortis had set in. The face and neck were of a deep purplish color, and the entire trunk and extremities had a pale bluish tint. There was moderate development of the subcutaneous fat. On opening the peritoneal cavity it was filled principally by several large distended loops of greenish congested

FIG. 1.—Multiple areas of cartilage and oil spaces.

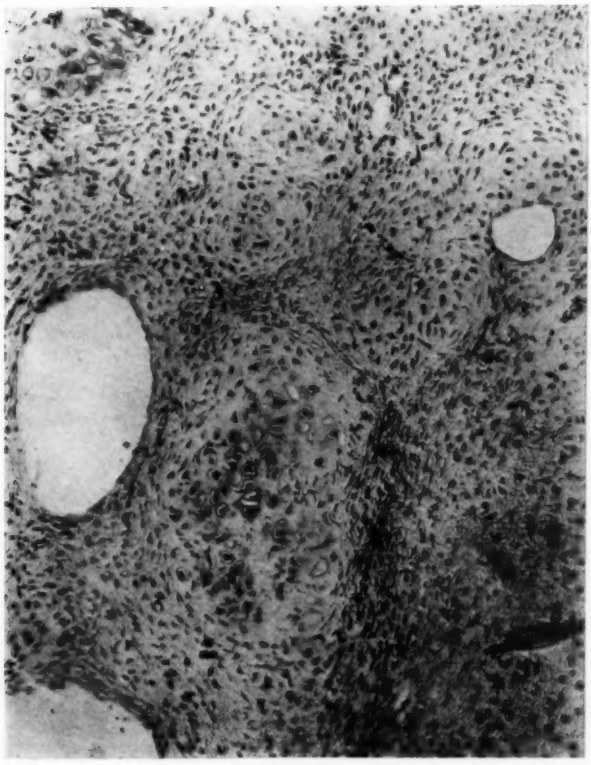


FIG. 2.—Transition of connective tissue cells to cartilage.

bowel. The cæcum was situated in about the mid-line, held loosely by a well developed mesentery. The appendix was normal except for position. In the left lower quadrant lay several coils of very nearly normal appearing intestine. The stomach was normal, but the duodenum, jejunum and a part of the ileum were enormously distended. This distention ended suddenly in a blind sac, from which extended several centimeters of obliterated bowel. The intestinal coils were bound together by fine fibrous adhesions. The pleural and pericardial cavities were normal.

Heart showed transposition, the apex being directed toward the right. On the outside no line of division can be seen between the ventricles. On opening the heart, both auricles were found to form a single cavity, as did also the ventricles.

Lungs were deeply congested. On section the anterior portions were of a pinkish red color, the posterior of a deep purple.

Kidneys were of normal size, showing well marked fœtal lobulations. The opaque gray cortex measures 2 mm. across. Running down the pyramids were orange yellow linear streaks.

Organs of neck.—The trachea and œsophagus were normal. The thyroid was large and nodular, and showed on section an increase in fibrous tissue.

Brain was negative.

Liver was slightly enlarged, measuring 9½ x 6 x 3 cm. Its surface was everywhere smooth and glistening, except where the duodenum was adherent to it. The organ was of a reddish brown color and of normal consistency. Running over the entire surface was seen a fine tracery of grayish lines. On section the parenchyma was of a yellowish red color, the center of the lobules having a slightly redder, the periphery a slightly more yellowish tint. About the lobules could be seen the same fine gray lines that were seen on the surface. The sulcus on the inferior surface of the liver in which the gall bladder and cystic duct were normally lodged, contained only a thin fibrous cord, 2 mm. in diameter and 3 cm. in length. It was impossible to dissect out the duct further than the hilum of the liver where it ended in a small knob which was connected also with the hepatic duct. The common bile duct could not be made out, but a well developed papilla of Vater was made out. An unsuccessful attempt was made to dissect up the duct from below. A very fine probe could be introduced for a distance of about 5 mm.

Spleen consisted of five distinct lobes; the largest four of these measured 2 x 2 x .4, 2 x 2 x 5, 2 x 1 x .4, and 5 x 6 x 3 cm. The grayish blue, rather firm lobes were loosely bound to one another. On section the pulp was of a brownish red color, and the Malpighian corpuscles just visible.

Pancreas was rather small. Its position was disturbed by the great dilatation of the duodenum, bringing it further anterior. On section the organ was of a grayish yellow color.

To describe more in detail, the malformation of the intestinal canal: the slightly dilated stomach measures 2 x 6 x 1 cm. The pylorus was normally situated, but was bound to the liver by fine fibrous adhesions; the stomach was also adherent to the spleen and to a portion of the dilated jejunum. A small portion only of the omentum remained attached to the greater curvature of the stomach. At a short distance from the pylorus, the duodenum measures 1 cm. in diameter. It was tightly bound for several centimeters to the under surface of the left lobe of the liver from where it arches back to the stomach. Extending directly downward for a distance of 7 cm. the gut rapidly increased in size, measuring at its lowest point 2½ cm. across. To its left surface, the cæcum and ascending colon were firmly adherent, to its right about 5 cm. of obliterated bowel and several loops of normal ileum. The duodeno-jejunal juncture could not be accurately determined because of the numerous adhesions and the fact that the duodenum was so greatly enlarged that instead of lying retroperitoneal it hung free in the peritoneal cavity and had a short mesentery. The jejunum next folded directly back and widened out into the large loop which occupied the greater part of the peritoneal cavity. It measured 24 cm. in length, and from 3½ to 4 cm. in diameter, and fibrous adhesions bound it to the upper portion of the duodenum. On both sides of this loop, portions of the obliterated bowel were adherent in regular undulations and covered completely by a thin layer of connective tissue. From the blind end of this loop, the small bowel continued as a small, dense fibrous band about 1 mm. in diameter which for a distance of 4 cm. was nothing more than a thin band of fibrous tissue. It then enlarged slightly and through the wall a white opaque mass about 7 cm. in length and 3 cm. across could be seen. This mass was soft and compressible and ended abruptly. The intestine continued as a thin cord 1 mm. thick for a distance of 3½ cm. Here the cord widened into a normal loop 1.7 cm. long and 4 cm. in diameter; it then narrowed down into a solid cord 1 mm. in diameter for a distance of 11 cm. to again widen out into a loop of normal ileum 3 cm. in length, and for a third time became a normal lumen filled with finely granular material. The obliterated portions were solid throughout.

Below this last constriction the bowel was practically normal, except for the adhesions which bound it to the structures mentioned above. The appendix measured 5 cm. in length and together with the ascending and transverse colon was located in the left lumbar region. The sigmoid and rectum were normal.

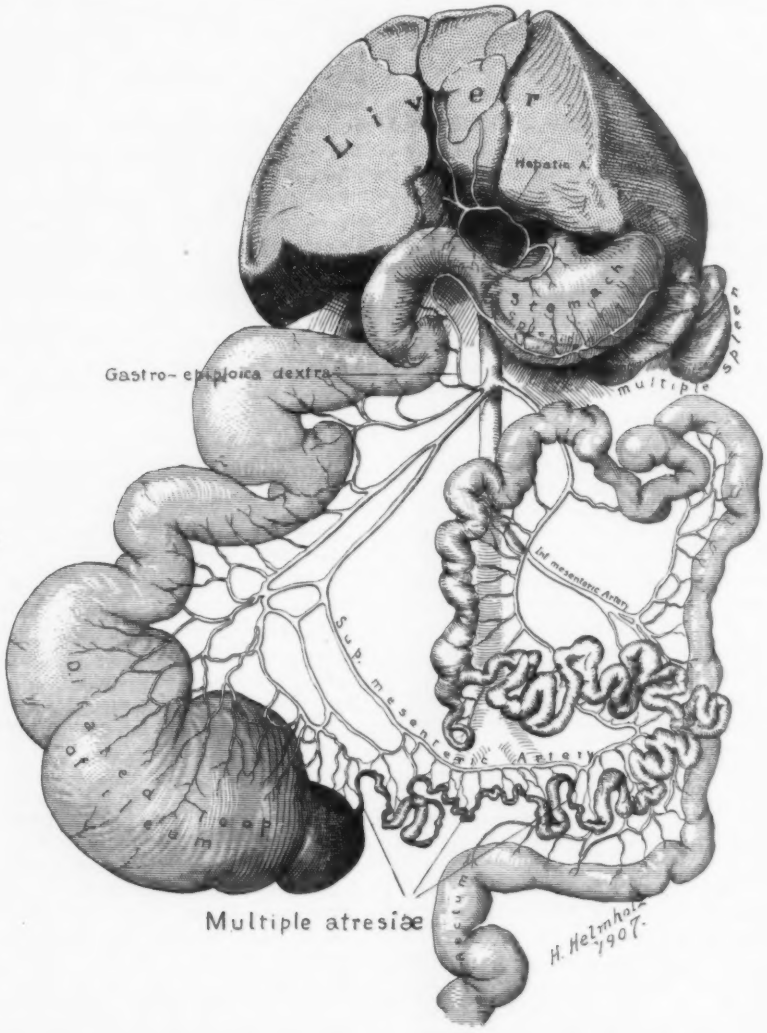
Cultures taken from the intestinal canal below the atresia showed the following:

Rectum at pelvic brim, several colonies, B. lactis aërogenes.
5 cm. above brim of pelvis, negative.
10 cm. above brim of pelvis, negative.
20 cm. above brim of pelvis, negative.
Ileo-cæcal valve, 1 colony B. acid formans.
Just below atresia, negative.
Mid-way between atresia and valve, negative.

The vascular supply.—The aorta was injected just above the diaphragm with vermillion gelatin. Note was taken of only the larger portal vessels, but no careful injection of that portion of the intestinal circulation was made. The cœliac axis came off from the aorta normally and immediately divided into the splenic and hepatic arteries; the gastric branch being given off by the hepatic as the latter passed by the cardiac orifice of the stomach in its course toward the hilum of the liver instead of as normal passing toward the pylorus and then sending back the pyloric branch to anastomose with the gastric. It then divided into a right and left hepatic branch. From the right were given off branches to the deformed gall bladder, to the pylorus and to the duodenum. The splenic artery ran upward and to the left, supplying no branches to the head of the pancreas and only a few small twigs to its tail. Near the spleen, it divided into five larger branches which supplied the larger of the lobes and sent small branches to the several smaller ones. One of the larger branches continued directly to the stomach and formed the gastro-epiploica sinistra which anastomosed with the dextra, a branch of the superior mesenteric. A number of small branches, the vasa brevia, were given off by the branches passing to the several lobes.

The superior mesenteric artery divided into three primary branches between which there were only a few anastomosing branches. The superior branch, a great enlargement of the pancreatic duodenal inferior, supplied the upper portion of the duodenum, and the greater curvature of the stomach, its terminal branch anastomosing with the gastro-epiploica sinistra; so that in this case the gastro-epiploic dextra was a branch of the superior mesenteric, a rather infrequent variation according to Quain. The middle branch can best be considered the continuation of the superior mesenteric, the inferior as the colica media; these two vessels formed one large loop, from which small vessels were given off directly to the intestinal, forming no arches and only

very scant anastomoses. This single vascular loop supplied the jejunum, the ileum, and the ascending and transverse colon. Instead of the 12 primary intestinal branches, the ileo-colic and the colica dextra, the entire number was merged into the single large loop. In the concavity of the largest loop of bowel there was a small plexus which might perhaps be considered an arch; the relations can be best seen by referring to the accompanying figure. The blood supply of the obliterated portion of the bowel differed in no way from that of the remainder of the ileum except that perhaps the vessels are of slightly smaller caliber. At the point where the intestine constricted suddenly to a fibrous cord, the vessels were delicate but quite numerous in the mesentery, and several fine branches supplied the bowel just beyond. Near and at the mesenteric border numerous anastomoses can be made out.



The colica media anastomosed as normal with the colica sinistra of the inferior mesenteric. The remainder of the blood supply to the intestinal canal was normal.

Microscopic Notes.

Lungs contained numerous areas in which the alveoli were filled with an exudate consisting largely of polymorphonuclear leucocytes, and some red blood cells and lymphocytes. The alveolar walls were thickened and congested. Many of the alveoli were filled with erythrocytes and serum.

Spleen.—The venules were distended with red corpuscles, their walls were, however, thin and delicate. The Malpighian corpuscles were normal.

Liver.—Corresponding to the tracery of fine gray lines seen in the gross there were seen bands of young cellular connective tissue running through the liver, for the most part connecting the portal spaces. The distribution of connective tissue was not uniform, but conformed fairly well to the type of annular cirrhosis. In the bands of fibrous tissue there were numerous lymphocytes and polyblastic wandering cells, and some proliferating bile ducts. The liver cells were swollen and fatty. In the hepatic capillaries were numerous blood-forming islands characterized by the small opaque nuclei tinged with hæmoglobin. A few club-shaped enlargements composed of liver cells with large vesicular nuclei were found. In the capillaries an occasional multilobulated nucleated cell of the megalokaryocytic type was seen.

Several sections through the fibrous strand (the remains of the gall bladder) showed that it consisted of a mass of fibrous tissue

in which were to be seen several cysts lined by cuboidal epithelium. No recent inflammatory tissue was made out.

Pancreas.—The arrangement of the lobulation was irregular because of a marked increase in fibrous tissue and the degeneration of the parenchyma. The islands of Langerhans were small and inconspicuous.

Kidneys.—The organs were congested, and at some points showed small hæmorrhagic areas. The epithelium was granular, but otherwise normal. At the cortex the glomeruli were still budding. The usual uric acid infarcts were found in the pyramids.

Thyroid.—The gland shows the same congestion that was everywhere seen and also a decided increase in fibrous tissue.

Testes were normal.

Intestines.—I. Serial sections of tip of large loop and first constriction.[1] The wall of the distended loop, in spite of its enormous enlargement, showed fairly normal structure. The epithelial lining had for the most part disappeared, but the villi had not been obliterated by the tension. At the point in the large loop that was continuous with the obliterated cord there was a small, shallow depression in the submucosa. The mucosa was, however, continuous over it, and did not extend into the fibrous mass. As compared with the normal intestine the muscular coats were slightly hypertrophied; both of the muscle coats of the obliterated portion were continuous with those of the dilated loop. The submucosa of the atrophic part consisted of a solid mass of cellular connective tissue, rich in vessels, but lacking an epithelial lined lumen. The slight enlargement seen in the gross as a white opaque mass proved microscopically to be an encysted cavity filled with a thick granular material that stained a uniform deep bluish purple with hæmatoxylin. No epithelial lining could be made out in the cavity, its wall consisted of a rather cellular connective tissue densely infiltrated with lymphocytes and a lesser number of leucocytes. The series of microscopical sections showed that the lumen did not extend out into the obliterated portion, but occasional small masses of this same material were found embedded in the wall of the cavity and for a short distance beyond at either end.

II. Serial section of a normal loop obliterated at either end. The conditions were essentially the same as in the first constriction. The mucosa was thrown up into typical valvulæ conniventes, shorter and broader than normal. The submucosa and muscular coats appeared normal. The lumen of the loop was filled with pink granular material. At neither end did the lumen extend out into the atrophic cords. At the one end, there was a small cup-shaped depression of the mucosa, at the other the mucosa does not even show this slight irregularity. The obliterated portions showed in none of the sections any sign of epithelium.

III. Cross sections of a small portion of the obliterated bowel. The series was cut especially to determine whether or not small islands of epithelium remained in the cord; in no section, however, were any epithelial cells found. Fibrous tissue had invaded the muscular coats surrounding the small central area of submucosa in which were several alveoli lined by flat endothelium and containing in some instances injection material. These were in all probability vascular spaces.

CASE II.—Baby A. Aet. 3 days. Died February 1, 1906.

Clinical history.—The infant was brought in 43 hours after birth because of the vomiting of bile stained mucous. It was the child of a healthy mother. The child was born at term, the only abnormality was a possible hydramnios. At the birth the abdomen was markedly distended, to relieve which it was given castor oil, and later sugar water. Large amounts of thick, dark green material were vomited shortly after birth; no blood was seen in the vomitus. The distention gradually increased and the bowels remained obstipated.

Physical examination.—The child was small and poorly nourished, its feet and hands were cold, and its pulse very weak. During the examination, the infant vomited 50 cc. of dark green fluid. No external malformations could be found. The abdomen was markedly distended, the veins were enlarged, and the skin cyanotic. No peristaltic waves were seen, nor masses felt. The walls were extremely tense. No dulness could be made out in the flanks. The anus showed no staining from meconium.

Operation.—January, 31, 1906, 10 p. m. The right rectus was incised and an opening made directly into a large cavity containing a considerable amount of greenish gray material, resembling meconium. At the lower end of the abscess cavity was a small opening leading into the general peritoneal cavity. Several enormously distended loops of intestine were traced down and were found to end blindly. A tube was sutured into the blind end of the intestine, and the large cavity packed and closed. The child died several hours after the operation. A complete section was not allowed, so the abdominal cavity was examined through the operation wound.

Anatomical diagnosis.—Congenital atresia of jejunum; diphtheritic enteritis with abscess formation; secondary inflammatory atresia; acute peritonitis.

The peritoneum was deeply injected and covered by fibrous adhesions. There was a slight amount of turbid fluid in the cavity.

The liver was of a purplish color, smooth on the surface and of normal consistency.

The stomach and duodenum were slightly distended, but otherwise showed no abnormalities. The jejunum, greatly distended so that in its widest portion it measured 1 cm. in diameter, ended blindly in a sac, which was of smaller diameter than the bowel some distance above it and was situated 50 cm. below the duodeno-jejunal juncture. The vascular distribution could not be worked out. Tracing the lower portion upward the rectum, sigmoid, and colon were collapsed and the appendix normal. Passing along the ileum upward from the ileo-cæcal valve, it was found to be twisted and its mesentery of very uneven length. The canal was patent up to within about 10 cm. of the large abscess cavity, that had been cut into at the operation, and was found to connect directly with the distal portion of the bowel. The constriction measures only about a millimeter in length, and had very much the appearance that would be produced by tying a string around the gut. It was impossible to pass a probe through this constriction. Above this point the intestinal walls were hypertrophied and thickened, and on passing upward gradually increased in diameter until the canal finally widened out into the lower posterior part of the above described abscess cavity.

This cavity was situated just behind the abdominal fascia and recti muscles, which formed its anterior wall. The remainder of the wall was made up partly of the dilated bowel and of fibrous tissue, the distinction between the two being hard to make out as the wall was for the most part necrotic and the muscular coats had in great part been displaced by fibrous tissue. No communication with the umbilicus, round ligament or urachus was made out. When collapsed, the cavity measured 8 x 7.2 cm. The wall was thin and elastic, and its inner surface was lined by a shaggy greenish, necrotic-looking membrane. To its posterior wall, the omentum was adherent, and also to the tip of the gall bladder.

The bladder and kidneys were normal.

The thorax was not examined.

Microscopical examination.—I. Serial sections of atresia below abscess. The intestinal canal above the atresia was lined by normal mucous membrane, thickened on the mesenteric border, and thinned out and compressed along the free border. The crypts of Lieberkühn along the latter border lay parallel to the wall; on the opposite side they formed a thick mass in which

[1] The series was unfortunately incomplete, so that only the grosser structures could be followed through.

there were numerous small cysts. The muscular wall showed the same relative condition, being two to three times as thick along the mesenteric border as along the free where the two muscle layers were often fused and indistinct. The serosa was greatly thickened by a large layer of cellular fibrous tissue in which numerous groups of lymphocytes and masses of yellow pigment were found.

In the serial sections the lumen gradually narrowed down, the same relation of thinned wall and compressed mucosa persisting. Little by little there developed an enlargement along the mesenteric border in the thickened muscle, forming a large mass in which the muscle fibers were arranged concentrically, and the center of which was in a section further along formed of loose fibrous tissue in which an epithelial-lined lumen gradually made its appearance. The muscle mass showed also the two distinct layers by this time. As the one lumen grew, the other diminished in size. There was no atresia, however, as was at first supposed. The lumen was continuous through the constriction, but was so flanked on both sides by valves made of fibrous tissue projections of the submucosa that any increase in pressure from above would only tend to obstruct more completely the thin slit-like channel.

To explain more in detail the arrangement of the valves. The two lumina lay side by side, and from one side of one and the opposite side of the other project folds of submucosa reaching almost across to the opposite side and having between them a slit-like epithelial lined lumen. This was, however, not complete throughout its entire length and ended in a mass of mucosa. Down to the point at which the upper lumen entirely disappeared the same relation holds true until finally the epithelial-lined lumen became only a mass of epithelium, still protected by a large single valve. As the pressure above increased the tendency would have been to more completely block the slit by the apposition of the valves.

II. Serial sections of the atresia above abscess.[2] The series demonstrated very clearly that the obliteration of the lumen was not a congenital malformation, but was secondary to an inflammatory process. The first sections showed the ileum to be a considerably dilated tube, the walls of which were hypertrophied and thickened by a great increase in fibrous tissue. The muscular coats extend only one-half way round the lumen, and then abruptly shade off into a mass of fibrous tissue which forms the entire thickness of the other half of the wall. The mucosa, submucosa, and muscular coats here have undergone complete necrosis, the remains of the muscular coats could just be made out by their arrangement in the peripheral portion of the necrotic zone, which was separated from the fibrous tissue by a zone that is thickly infiltrated with polymorphonuclear leucocytes, and red blood cells. The lumen at first was an irregular slit about 3 mm. in length, about three-fifths of which was lined by almost normal mucosa, the remainder by a necrotic diphtheritic membrane including practically all that remained of the normal intestinal wall. A portion of the lumen toward the normal side then became constricted, continuing as a round lumen, and gradually disappeared from the sections.

The lumen became still further constricted by the bulging inward of the diphtheritic membrane, converting it into a crescent-shaped slit. Continuing the series a larger and larger portion of the wall became involved in the process and finally the entire mucosa was replaced by a necrotic diphtheritic membrane, which was completely surrounded by a dense mass of fibrous tissue. There remained a small amount of smooth muscle lying somewhat apart, however still showing the circular layer and the longitudinal running at right angles to it and surrounding it on two sides. About ten sections further along the last traces of muscle have disappeared. The lumen by this time was obscured and practically obliterated by a mass of necrotic material infiltrated by leucocytes. In the surrounding connective tissue there were many polyblasts loaded with blood pigment, and also some small hæmorrhages. At one point the necrosis extended almost to the peritoneal surface. Still further along the lumen became entirely obliterated by the ingrowth of connective tissue and only remained as a solid mass of acute inflammatory tissue with a central hyaline mass of necrosis; this later faded out into a delicate fibrous tissue in which all signs of an intestinal canal are lost. The bowel above the lower atresia was enlarged and the muscle hypertrophied. The mucosa was practically normal except for slight thinning toward one side. There was some variation in the thickness of the muscle layers, especially of the external. Passing upward toward the abscess, the bowel becomes still further dilated, the muscular coats thickened, and the submucosa made up of a delicate fibrous tissue. In the mucosa, there are numerous hæmorrhages. On the serous surface, there was an acute organizing peritonitis which had in places completely destroyed the external muscle layer.

Sections taken through the abscess wall including the cross section of the ileum as it leaves the cavity showed a very marked destruction of tissue. The wall on one side was made up of rather sclerotic fibrous tissue lined by a necrotic membrane; the other side was completely necrotic, showing numerous large vessels filled with red blood corpuscles, and there were also numerous red cells in the tissues suggesting the appearance of an hæmorrhagic infarct. This same portion of the wall helped to enclose on its other side an abscess cavity, the remainder of the abscess wall being formed by two loops of intestine closely adherent to one another. The one intestinal loop has undergone complete necrosis, the other on the side opposite to the abscess cavity has a large necrotic zone replacing the mucosa, and this was surrounded by a muscular layer infiltrated with fibrous tissue. The fibrous tissue contains considerable blood pigment.

The kidney, the only other organ saved for microscopical examination, showed nothing abnormal.

To come back to the etiological factors in the two above described cases. Case I is a very typical case of multiple atresia, as described in a great number of instances, except that the peritoneal adhesions and other signs of infection are more marked features than are usually found. The plate does not give any idea of how the intestinal loops were closely bound by fibrous adhesions, especially the completeness with which the obliterated portions of the bowel were literally plastered to the mesentery of the large loops and covered by a thin layer of fibrous tissue. Other evidence of early fœtal inflammation is the peculiar character of the mesenteric blood supply. As is well known, in the fœtus there are a very great number of anastomosing arches which are gradually obliterated during the fœtal life until the normal number of arches remain. In this case, on account of inflammatory changes, there has been an excessive destruction of arches leaving only a single large loop from which the branches pass directly to the intestine. Whether the change in the blood supply is the cause (as suggested by Wyss) or the result in these cases, can in this instance be settled in favor of the latter. At the point of the uppermost atresia, there is a more

[2] The sections include the portion of bowel just above and the beginning of the obliterated bowel.

nearly normal arrangement of vessels, than almost anywhere else along the course of the intestinal canal and though the vessels are smaller than normal, their caliber is better explained by loss of function of the part than by congenital malformation. A second accessory factor is the well developed cirrhosis of the liver, which can be most easily explained as secondary to the blocking of the bile ducts. A cirrhosis of the annular type, not of syphilitic origin, is a very unusual find in a child at birth. The cirrhosis of the pancreas is best explained in like manner. To determine whether the atresia of the bile duct and bladder was inflammatory or developmental was not possible with any degree of certainty, but with the evidence so marked for a fœtal peritonitis, it seems probable that this obstruction was a part of the same process.

Kreuter, in his article on this subject, makes the assertion that in practically every case the atresia was due to a persistance of the fœtal atresia found normally between the 5th and 10th week. This, however, cannot be considered a cause of the atresia as one would be led to believe, but merely the process by which it takes place, and although it is a step forward in explaining how the atresia may occur, it can hardly be called an etiological factor. That a peritonitis might cause a persistance of the embryonic atresia seems possible, but not probable because of the early stage at which embryonic atresia occurs. How to account for the disappearance of the epithelium without inflammation and necrosis seems a difficult task.

Case II illustrated perhaps better than any case yet described the results which may follow atresia. The lower atresia can most readily be explained by supposing that the valves which practically formed a complete obstruction were produced by an outgrowth of fibrous tissue into a mass of epithelium which for a certain time during the second month occludes the lumen. Kreuter has mentioned the change of character in the epithelium when it grew in solid masses and its resemblance to round cells and its return to normal as soon as lumina were formed. That this is true of adult epithelium as well, can be shown in experiments on the rectal mucosa, epithelial downgrowths taking the squamous type and returning to the cylindrical only when lining a lumen. Secondary to an intense infection which led to the formation of an abscess, a possible infarction and an inflammatory atresia followed in which the process can be definitely traced. This inflammatory atresia is not a single instance, but can be classified with several others reported in the literature. Marchwald reported the finding of cocci with Gram's stain in a mass of hyaline necrotic tissue secondary to a diphtheritic enteritis. Thorel reported ulceration and diphtheritic inflammation, and Kirchner found an enteritis and peritonitis.

The fact that the intestinal canal opened right out into the abscess makes it seem that it as well as the atresia was just part of the general process, a diphtheritic inflammation with perhaps a secondary thrombosis which has completely destroyed the intestinal canal and widened it out into this large abscess cavity on the one hand, and on the other led to an atresia.

In summing up the etiological factors in 185 reported cases of congenital atresia of the small intestine, Kuliga disputes in turn the bearing of each one of the described etiological factors, but he has no explanation or explanations to offer in their stead, and leaves one in a very uncertain state of mind when one gets to the end of his article. It seems of greater value to explain the facts as logically as possible, with the known factors, rather than give no explanation at all. Since Kuliga's summary there have been fourteen cases reported, including the two herein described. Case III of Chiari's series is of interest because of the necrotic intussusceptum found on microscopic examination. Howell found that the distal portion of the bowel had intussuscepted itself for a distance of about two inches. Karpa also gives fœtal intussusception as the cause of the obliteration found in his case. Wernstadt explains the atresia in his case by the persistance of the embryonic intestinal atresia. In two of the other cases Edington and Clogg, Case I, give excessive obliteration of Maeckels' diverticulum as cause of the atresia. In the six other cases no definite etiological factor is given.

Thus in 14 cases three (21 per cent) are reported definitely due to intussusception, which is a large percentage when compared with one per cent in Kuliga's statistics.

In conclusion it is urged that more complete histological studies be made in all cases, so that the relative importance of the various factors be determined. I should like to thank Dr. Whipple for turning these two interesting cases over to me, and Dr. Sowers for his notes on Case II.

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A SYNCYTIOMATOUS TUMOR OF THE STOMACH.

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The very interesting histological features of this tumor of the stomach, made it seem of sufficient value to report it as an individual case. Though in all probability a number of similar cases have been reported, it is impossible to cull them out by the titles given in Catalogue of the Surgeon General's Library. This tumor has been called *syncytiomatous* because of its resemblance in many areas to syncytium, in the hope that until a better term is applied, the cases of this kind may be brought together under this head.

Clinical Note.—L. M. Black. Aet. 40 years. Admitted October 29, 1906, to the Johns Hopkins Hospital, complaining of pain in stomach.

Past history.—Constipated for many years. Syphilis at 24. Lost 36 pounds in last year.

Present illness.—During September patient began to feel poorly and lose his appetite. On October 1, 1906, while at supper, had a sudden stabbing pain in the epigastrium and feeling of nausea. After vomiting pain ceased. For five days vomited about one-half hour after each meal. No pain after eating since.

Physical examination.—Marked fullness of epigastrium extending to within 3 cm. of ensiform cartilage; definite edge to be made out. Spleen 2 cm. below costal margin. Test meal: Free HCl. No sarcinæ or yeast cells. On surface to right large nodules are distinctly palpable. In the mid-line the liver extends 14 cm. below the tip of the ensiform.

Clinical diagnosis.—Abdominal tumor (liver?), lues (?), cancer (?).

The post-mortem examination was made two hours after death. The section was No. 2807 of the Johns Hopkins Hospital pathological series.

The anatomical diagnosis was: Syncytiomatous tumor of stomach; metastases to gastro-hepatic, mesenteric, anterior mediastinal glands, liver, spleen, and lung; direct extention to pancreas and colon; ascites and generalized peritonitis; chronic fibrous myocarditis; calcified sub-pleural tubercle; chronic fibrous pleuritis of left side; acute interacinar pancreatitis; chronic diffuse nephritis; chronic lepto-meningitis; ossification of falx cerebri.

Body is that of a very emaciated negro, measuring 167 cm. in length. The body is still warm. Rigor mortis marked. The pupils are equal and dilated. The abdomen is markedly distended, and in the left hypochondriac region a firm, hard mass can be felt. On opening the peritoneal cavity about 1200 cc. of yellow turbid fluid, containing numerous shreds of fibrin were obtained. Everywhere the peritoneal surfaces are covered by small shreds of fibrin. The liver is enormously enlarged, extending 10 cm. below the costal margin in the right mamillary line, in the mid-line 19 cm. below the xiphoid cartilage, and in the left mamillary 8 cm. below the margin of the ribs. The gall bladder is exactly in the mid-line. The surface of the liver is very irregular, showing numerous white and a few reddish elevations, its superior surface is bound down to the parietal peritoneum, and to the diaphragm by a mass of rather firm fibrous adhesions. In the suspensory ligament and in the parietal peritoneum there were several firm, yellowish gray nodules of the same general character as those in the liver. The enlarged liver has displaced the stomach downward into the lumbar region, where it forms a large firm mass, adherent to the colon and the retroperitoneal structures. The spleen is everywhere bound down tightly by adhesions. On the right the diaphragm extends to the fourth rib, on the left to the fourth interspace. The right pleural cavity is completely obliterated by dense fibrous adhesions, the left is entirely free. In the pericardium there is a slight excess of clear straw-colored fluid.

The *heart* is slightly enlarged, weighing 300 gm. Its surfaces are everywhere smooth and glistening. On the posterior surface of the left ventricle there is a large yellowish gray patch, measuring 3 x 1½ cm. On opening the heart the valves are all found delicate and competent. The right ventricular wall measures 5 mm. across, the left 2 cm. Extending from the septum to the papillary muscles in the left heart are several moderator bands, and from its upper portion extends a muscular bundle 5 mm. thick to the anterior wall, arching through the cavity. The posterior wall of the left ventricle has a rather grayish appearance, and is considerably thinner than the rest of the ventricle. On section it measures 4 mm. across and consists to a large extent of only fibrous tissue. The base of the aorta is markedly sclerotic, especially about the orifice of the coronaries. The opening of the right cannot be made out, as it is involved in a thick, yellowish gray patch of sclerosis. On passing a probe through the coronary from a distal point, it emerges in a small slit right in the middle of the patch. The coronary vessels also show marked sclerosis.

Lungs.—The right lung is collapsed and everywhere covered with shaggy adhesions. At one point along the anterior margin there is a fibrous thickening, partially calcified and containing thick granular material. Several other small grayish nodules are seen on the cut section. The bronchi and larger vessels at the hilum are clear. The left lung is smooth on the surface and on section is of a pinkish yellow color, and shows no areas of consolidation.

Spleen measures 9 x 5½ x 2½ cm., and weighs 95 gm. The organ is of a grayish blue color and its capsule is wrinkled and covered by old fibrous adhesions. On section there is a slight increase in fibrous tissue, the Malpighian corpuscles are just visible, and at one point there is a small grayish granular nodule measuring 4 cm. in diameter.

Kidneys weigh 250 gm. The left kidney measures 10 x 7½ x 2½ cm. The capsule strips readily, leaving a uniform yellowish red surface, on which the dilated stellate veins, and small red retracted patches stand out very prominently. On section the cortex measures 6 cm. across, and the striations are quite regular. The right kidney measures 9½ x 5½ x 2 cm. The capsule strips readily except at one pole where it is firmly adherent to a large depressed area. On section of this area the striations and glomeruli are absent, and the cortex measures but 1 cm. across.

Stomach measured roughly 17 x 7 cm. The organ is firmly bound to the retroperitoneal structures and colon. The tumor involves the pyloric antrum and the lesser and greater curvature for a distance of about 10 cm. The mass is exceedingly firm and hard; the anterior wall does not collapse on allowing the air to escape from the stomach. Situated in the lesser curvature are several large, firm, yellowish glands, and one large reddish yellow mass, measuring 5 x 4½ x 3½ cm. and of very much softer consistency than the yellow nodules. Hanging from the greater curvature near the cardiac end there is a similar reddish-yellow mass, which measured 5 x 3½ x 2 cm., and resembled the one in the lesser curvature. On opening the stomach along the greater curvature the tumor is seen to involve the stomach 12 cm. inward from the pylorus and completely encircles it. In the central portion of the tumor is a large ulcerated area measuring about 3 cm. across; its base is clean and smooth and mottled red and yellow,

its edges are smooth and rounded off. Extending outward in the submucosa from this central area are numerous finger-like processes, which gradually shade off into the normal stomach wall. In several spots over these processes the mucosa has been destroyed, leaving small ulcerations which, like the large ulcer, have a smooth base and clean rounded edges.

The thickness of a cross section of the tumor in the central ulcerated area is ½ cm., and toward the periphery shades off gradually into the normal thickness of the stomach wall. The tumor consists of irregular lobulations of varying shades of yellow and gray, alternating with dark red, apparently hæmorrhagic, areas. Definite distinction between epithelium and stroma cannot be made out. The entire mass has the appearance of a uniform tissue in which necrosis and hæmorrhage has produced a variety of colors. The more peripheral portions of the tumor on section are of an opaque grayish color and can be seen invading the submucosa and muscular coats. The large masses at the lesser and greater curvature on section are of a uniform pinkish yellow color, and at their margins show numerous hæmorrhagic areas. Section of the other nodules show them to be of a uniform grayish yellow color, rather granular and friable, and presenting some areas of softening.

Pancreas is firmly adherent to the tumor mass, and also to the large mass at the lesser curvature. The organ has been invaded along its middle third, without any very deep extention down into it. The tumor tissue, of a mottled grayish white and reddish color, stands out sharply from the translucent pinkish yellow pancreatic parenchyma. The organ is otherwise normal.

Liver is greatly enlarged, measuring 24 x 30 x 11 cm. and weighs 4070 gm. Its surface is covered over by a thick coating of fresh fibrinous adhesions, and is studded with metastases which are of two distinct types: the one rather firm, of a uniform yellowish gray color, and irregular edge, the other soft and elastic, of a reddish brown color with occasional yellowish gray area in it. These metastases vary in diameter from 1 to 2½ cm. In the folds of the suspensory ligament and adherent to the gall bladder there are found several yellowish opaque metatastic nodules. On section metastases thickly stud the liver substance, involving more than half of the surface. The metastases have the same character as those described on the surface. The yellow type is much the larger in size, one conglomerate nodule measuring 5½ x 6 cm. The center of the larger nodules has become softened and necrotic, and in some only a few strands can be seen passing across the depressed necrotic center. The nodules are evenly finely granular, and no definite stroma can be made out; there is, however, a slight lobulation to be made out in the larger nodules. The brownish red nodules show a more definite arrangement. There is a rather coarse network of pinkish yellow anastomosing bands of stroma dividing the growth into various sized lobules of a deep reddish brown color. There are all transitions between the two types of metastases. The small 1 cm. nodules also show the two types, so that the one cannot be a degeneration of the other. The liver tissue is of a yellowish brown color, the lobulation well marked by a slightly redder tint of the central portion of the lobules.

On the wall of the portal vein, numerous small metastic nodules are seen, sometimes as a large single nodule measuring 1 to 2 cm. across, or as a little cluster of pin-head-sized nodules covering an area of about 5 x .3 cm.

Intestine.—The small intestine is practically normal; the large intestine, except for adhesions to the tumor in the transverse colon, is the same.

Bladder, *prostate*, *seminal vesicles* and *testes* normal.

Aorta shows very marked arterio sclerotic thickenings. In the abdominal aorta the process has gone on to calcification and ulceration.

Brain.—The pia arachnoid is greatly thickened over the cortex, especially along the longitudinal fissure. The falx cerebri is almost completely ossified.

MICROSCOPICAL NOTES.

Heart.—The muscle fibers are hypertrophied, but in areas have undergone a granulative degeneration and have been replaced by fibrous tissue. The endocardium is considerably thickened.

Lungs.—The alveoli are free of exudate and the lungs, except for several tumor metastases, are normal. These nodules are found exclusively in and extending out from the blood-vessels. Quite a number of the smaller arteries are plugged by masses of tumor cells and one vessel is lined by tumor cells, but still contains red blood corpuscles. The largest of the metastases is in connection with a large vessel which is completely filled up with tumor cells. The metastasis shows several areas of degeneration, and the cells contain large and irregular nuclei. At one end is a thin, crescent-shaped space, which is all that remains of the lumen of the vessel. The tumor spreading out into the alveoli has an irregular alveolar arrangement without sharp definition between stroma and tumor cells. In this area are several vessels stuffed with tumor cells. The cells are very irregular in size and take almost any shape. Their nuclei vary greatly in size; a large, spindle-shaped, vesicular nucleus is the most common, but large masses of nuclear material and giant cells are seen.

Spleen.—The capsule and trabeculæ and also the walls of the venules show an increase in fibrous tissue. The change is noted in the Malpighian corpuscles. The metastases are very small, and for the most part seem of very recent origin, in that they lie free in the blood spaces in small groups of from ten to a dozen cells. The individual cells cannot be distinctly recognized, and no stroma can be seen in these small metastases or in the larger one. A single mitotic figure was found.

Pancreas.—The pancreas is compressed and invaded by the tumor growth. Throughout there is an increase in the connective tissue, especially marked toward the tumor. In one portion the pancreatic parenchyma is undergoing a rapid degeneration; there is a great out-wandering of leucocytes and lymphocytes into the acini. The white blood cells are especially numerous along the newly developed strands of fibrous tissue. In one acinus as many as 20 polymorphonuclear cells are crowded; the epithelial cells are either drawn out and atrophic, or have entirely disappeared. In other areas portions of acini have undergone hyaline necrosis. Lying free in one of the larger splenic veins are a group of tumor cells. The islands of Langerhans are unchanged.

Kidney.—The cortex is irregular and consists in the depressed areas of a cellular vascular connective tissue in which some few sclerotic glomeruli and atrophic tubules remain. The convoluted tubules are swollen and contain granular material, their epithelium shows parenchymatous degeneration. The renal arteries show a marked degree of thickening. No tumor metastases are found.

Aorta.—The intima is enormously thickened and degenerated. Over a large portion of it there is a fresh thrombus mass. The greater part has undergone necrosis, showing no nuclei, but great numbers of cholesterin crystal spaces. The middle of the ulcer, in a little cup-shaped depression, has extended through almost the entire wall of the aorta. It is covered over by a calcified plaque, separating this secondary degeneration from the rest. The media further shows numerous areas of cellular infiltration, extending through its entire diameter. The lumina of the vasa vasorum are in many of the vessels almost obliterated.

The *adrenal* appeared normal.

Stomach.—Sections taken through the tumor in the ulcerated area show that practically the entire wall is made up of tumor cells, leaving only a few muscle bundles intact. The mucosa narrows down somewhat and is infiltrated with lymphocytes, but

otherwise is perfectly normal, even up to the very edge of the ulcer. The epithelium shows no signs of a malignant change, and the edge of the ulcer is thin and delicate, showing no changes similar to those seen in the rolled-over edge of a carcinomatous growth. In another section the mucosa overhangs the tumor growth for a short distance, and nowhere shows anything but normal cylindrical epithelium. At a short distance from the ulceration there is an invasion of the mucosa by the tumor, which breaks through the muscularis mucosa. The mucosa in its lower portion consists of a small mass of tumor cells, which have almost entirely destroyed the gland tubules, between which they grow up almost to the surface. The cells are very irregular in their character, a number of acini having the light staining reaction of the hypernephroma cells. The tumor cells have extended almost to the surface and would soon produce an ulceration in much the same manner that the others were no doubt produced. At another point a little further along the growth has extended through the muscularis, but has not invaded the mucosa. In sections taken from the more outlying parts of the tumor the mucosa is everywhere normal.

The tumor apparently originates in the submucosa or muscularis, as nowhere can any relation be made out to the gastric epithelium. In the central portion of the tumor, submucosa and muscular coats are not distinguishable, the entire wall consisting of tumor tissue which shows great variation in its structure. A striking feature is the amount of degeneration that is present, though not surprising on account of the slight amount of stroma that is present in the tumor.

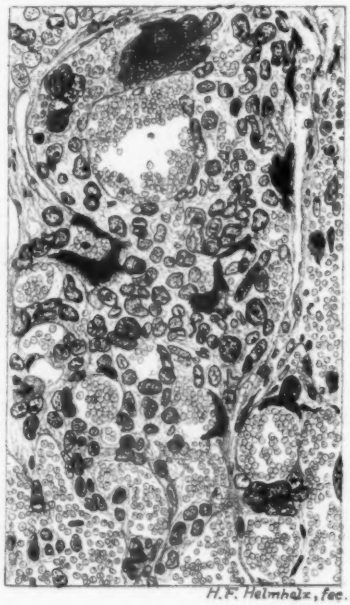
Bands of connective tissue divide the tumor into irregular lobules, which differ considerably in character. The larger part consists of rather irregular sized cells of distinct outline, containing large nuclei, often several, sometimes vesicular, sometimes pyknotic. From this general type there are all transitions to areas in which there are no cell outlines whatever, the protoplasm forming large pink masses, containing nuclear masses which consist of anywhere from 5 to 15 nuclei, that vary greatly in size, some being small and deeply staining, others light with only a few chromatin granules. Only a few mitotic figures are found in such areas, and the frequent areas of necrosis are a further proof that some of these changes are degenerative. Some of these large cells appear to have large nuclei that are not formed by nuclear apposition and they can often be seen lining capillaries.

The relation of the tumor cell to the circulation is very intimate. All through the tumor, usually in lobules, there are blood spaces that are lined directly by tumor cells. This is true not only of the large spaces in the epithelial masses, but also of the capillaries that run in the stroma. They are lined on one side by a normal looking endothelial cell, on the other by a multinucleated mass of protoplasm, and some areas are made up entirely of small vessels lined by tumor cells, and often partly filled with tumor cells.

Quite as characteristic as these are other areas in which the tumor cells take on the type of fibroblasts, forming large, thin-drawn-out cells that run together in bundles, and show all the transitions to the ordinary fibroblast. These areas form only a small part of the growth and are found in the lower portion of the tumor. Mallory's connective tissue stain shows that there are but very few connective tissue fibers in these areas. One area in particular is of interest because of the very great size of the cells, their enormous nuclei in some instances being multiple nuclei. Their protoplasm stains pink, is slightly granular, and shows no striations.

Extending outward in the submucosa, the tumor has markedly involved it and the muscular coat for a considerable distance. The character of the growth is very different. It has grown in small solid acini, as a rule, consisting of from four to ten cells and occasionally in larger epithelial masses. The cells show the same tendency to form multinuclear cells.

Liver.—The liver metastases not only repeat in every detail the original growth in the stomach, but accentuate more distinctly the difference of arrangement described above. In particular are the vascular relations well shown; very peculiar pictures are seen, such as a blood-vessel about 30 mm. across crowded full of red cells, and apparently surrounded by a single cell, the nucleus of which is enormous, extending almost one-half way around the vessel. The accompanying drawing is taken from the same metastasis. It shows the intimate relation of tumor cell and blood current, large multinuclear cells lying practically free in the vessel. The large pyknotic masses of nuclear material are a very prominent feature.



Some areas have a very definite alveolar arrangement, more so than the original growth.

The necroses are also very much more extensive; almost the entire metastasis in some instances is necrotic, only the outer margin remaining intact. As seen in the gross, there is a vein completely occluded by tumor cells.

The liver is markedly congested and the cells atrophic.

The individual cell characteristics are very varied; the predominent cell is a rather small cell with a large nucleus, without any very definite cell outlines, forming irregular masses of cells, the nuclei of which often are massed together to form large clumps. A fine stroma pervades the growth. Mitoses are very frequent; especially large and irregular ones are seen along the margin of several of the small metastases.

The classification of this tumor offers some difficulty. At the post-mortem examination it was supposed to be a carcinoma, with very unusual hæmorrhagic tendencies; the microscopic examination, however, did not support this view.

The edge of the ulcer was slightly overhanging, and the epithelium of the mucosa had no relation whatever to the tumor. Several other invasions of the mucosa show how in all probability the large central, and the many smaller ones were produced.

The microscopic examination showed a tumor that was not to be sharply classified as carcinoma or sarcoma. The cells, al-

though they resembled epithelial cells, were not sharply defined, and had the tendency to form masses and groups which seemed to run together to form large multinuclear cells, and large deep blue staining nuclear masses. In their relation to the circulation they could only be compared to endothelial cells, as they definitely line blood spaces and capillaries, and apparently intermediate stages can be readily found.

The stroma is of very fine character without any definite bearing, except that in several sarcomatous-like areas there appears to be direct transition from tumor cell to fibroblast. The cells show a great tendency to necrosis and the tumor to a hæmorrhagic degeneration.

The metastases resemble carcinoma in that they pass along the lymph channels, and sarcoma in that they have traveled along the blood stream to liver, lungs, and spleen. The vascular metastases in the larger vessels of the liver are of some interest.

The tumor, it seems to the author, may be supposed to have arisen from a misplaced "anlage" in the stomach wall, and because of the syncytial character of the cells may be called a syncytiomatous tumor.

THE RELATION OF INTESTINAL INFECTION TO VISCERAL TUBERCULOSIS.

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The object of this paper is to present some facts which speak against the theory that the intestinal tract is the portal of entry in a large number of infections with tuberculosis. When such intestinal infections do occur the mesenteric glands are invariably diseased, and when, after a careful examination of these glands, we find them free from any tuberculous process, a definite conclusion may be drawn that the intestinal tract was not the portal of entry.

In a previous communication (1) a series of cases was given in many of which tubercle bacilli were found in the thoracic duct. The intestines and mesenteric glands were examined. The series now numbers 47 cases, and may be grouped as follows:

1. *Acute miliary tuberculosis*—5 cases. Two cases showed vascular foci of distribution, but in addition intestinal ulcers and tuberculous mesenteric glands. The duct smears showed many tubercle bacilli. Three cases showed invasion of the thoracic ducts by the tuberculous process, and the intima in every case was sanded with great numbers of minute tubercles. Duct smears in these cases showed hundreds of bacilli in a single field of the microscope. The first of these three cases presented a caseous salpingitis with extension to the pelvic and retroperitoneal glands, one of the latter rupturing into the receptaculum. The lungs were full of miliary tubercles but there was no cavity present. The second case presented a small plumonary cavity, no intestinal ulcers, but large caseous mesenteric glands, many of them clustered about the receptaculum. No rupture of a gland into the receptaculum was demonstrated. The viscera were full of tubercles. The third case was almost identical with the second, and here the cavity was even smaller, but very rapidly growing with extensive gelatinous broncho-pneumonia. No intestinal ulcers but large caseous mesenteric glands were found.

2. *Subacute tuberculosis.*—(a) 2 cases of Pott's disease of the lumbar region, with involvement of the retroperitoneal glands, and a few disseminated tubercles in the viscera. No lung cavities nor intestinal ulcers. The duct smears were negative although it seems probable that the tubercles in the viscera were due to bacilli which were swept through the duct. (b) 28 cases of pulmonary tuberculosis with cavity formation, and many or few disseminated tubercles in the viscera. Duct smears were positive in 20 cases, at times only two or three bacilli being found after long search, again forty or fifty on a single slide. In these 20 cases the mesenteric glands invariably showed a tuberculous process, usually caseation, while the intestinal tract showed ulcerations in 16 cases. 6 of the 8 cases, which showed no tubercle bacilli in the duct smears, had intestinal involvement, and in all 8 there were tuberculous mesenteric glands. 2 of the cases with bacilli in the duct showed only microscopic disseminated tubercles which were not visible to the eye. This group emphasizes the importance of the thoracic duct as a distributing agent in the cases which show scattered tubercles in the viscera, and tuberculous mesenteric glands.

3. *Chronic tuberculosis*—12 cases of chronic pulmonary tuberculosis with cavity formation, but no disseminated tubercles in the viscera. 8 cases had tuberculous mesenteric glands, while but 5 showed intestinal ulceration. One case showed only two small ulcers in the appendix with a caseous gland at the ileocæcal fold in the mesentery. 4 cases showed neither ulcers nor tuberculous glands.

When one considers the fact that three of this last group were insane patients who swallowed most of their sputum, which was profuse, coming from large apical cavities, that one of the insane cases showed only a small intestinal ulcer, and a caseous mesenteric gland, while another showed only a few tuberculous mesenteric glands and the third no such lesions, it seems clear that the intestinal tract of adults does not absorb the tubercle bacillus very readily. It seems probable that bacilli can pass through a mucosa, which to the eye at least seems intact, but are filtered out of the lymph stream by the glands in the mesentery. These bacilli produce lesions in the glands which plainly mark the course of the infection, and probably the bacilli in the duct smears are derived from these secondary mesenteric foci rather than from the intestine.

During the last 500 autopsies 3 cases were found which showed a calcified mesenteric gland, no intestinal ulcers, a few pigmented fibrous or calcified pulmonary lesions, and tuberculous bronchial glands. In such cases the infection may have been through the intestinal tract, but not surely. When

one considers how common are the findings of healed pulmonary lesions in the routine autopsies, and how infrequent are tuberculous mesenteric foci in such cases, it seems reasonable to conclude that such infections do not take place through the alimentary tract, or at least very rarely. When we study the cases with extensive pulmonary cavities we often find tuberculous mesenteric glands which may be secondary to the pulmonary lesions, or may be primary, and mark the course of an alimentary infection. But comparing this group of cases with that showing slight or early lesions with no pulmonary cavities, we are forced to conclude that the chances are against a primary intestinal infection.

It is of interest to compare this group of cases with a series of hogs in which the distribution of tuberculous lesions was studied. These animals were observed at an abattoir near the laboratory. They averaged from 8 to 10 months of age, 120 to 150 pounds in weight, and were shipped from the middle west where many of them had fed behind cattle. The animals were very healthy as a rule, and the percentage of animals infected with tuberculosis rarely exceeded 3 per cent.

The lesions were usually limited to a few glands, and the cases may be grouped as follows:

1. *Acute miliary tuberculosis*—3 cases. All showed caseous mesenteric and submaxillary glands, the latter often measuring 3 cm. in diameter, and showing complete caseation with slight calcification. The viscera were sprinkled with small tubercles, and the lungs showed small areas of tuberculous bronchopneumonia. One case showed a few small cavities in the lungs, and an ulcer near the cæcum. The ducts could not be examined. Through the kindness of Dr. Mohler, Chief of Pathological Division, Bureau of Animal Industry, I was able to examine five other cases in Washington which resembled closely the cases described. The intestines were not examined, but the submaxillary and mesenteric glands were invariably diseased, and showed the most extensive lesions. The organs showed numbers of small tubercles, and the lungs small patches of tuberculous broncho-pneumonia.

2. *Subacute tuberculosis*—5 cases. All but one had caseous submaxillary glands, and that one showed tuberculosis of the mesenteric glands round the duodenum. Three cases had caseous mesenteric glands. The intestines were not carefully examined, but no conspicuous ulcers were present. The lungs, spleen, or liver showed a few tubercles of varying sizes. No lung cavities were seen.

3. *Local tuberculosis*—14 cases. All but one of these showed tuberculosis of the submaxillary glands, and five mesenteric tuberculosis localized in one or two glands. Such cases make up the greater part of the infections, and many more were seen at the abattoir, but not carefully examined. These animals were all young, and gave an excellent opportunity for the study of the early lesions. Many of them had been fed behind cattle, and probably were infected from them through the food, there being no cases in which the oldest lesion was found in the lungs.

In all cases the channel of infection was marked by a tuberculous gland, either submaxillary or mesenteric. It is remarkable how frequently the submaxillary gland was involved (20 out of 22 cases), and indicates the pharynx as a common and easy portal of entrance for tuberculosis in the case of the growing hog. The findings in this series of cases agree closely with those of Schroeder and Mohler (2), who produced experimental tuberculosis in hogs by feeding. Their tabulated experiments are valuable, and support the conclusions drawn from this work, but their own conclusions are somewhat different. These observations parallel those in children who, it is well known, are more frequently affected with mesenteric tuberculosis (Henke) (3). Children with cervical tuberculous glands in many cases show a tuberculous process in the pharyngeal adenoid tissue (White) (4).

An attempt was made to trace in the common laboratory animals the course of infection from the intestinal tract, and the rapidity of its advance through the mesenteric lymphatics. Owing to an epidemic of pneumonia among the animals used in these experiments the series is incomplete, but the findings will be given briefly as they support the deductions drawn from the preceding cases in men and hogs.

Two cultures of the tubercle bacillus were used in these experiments: one obtained through the kindness of Dr. Theobald Smith—a bovine organism of medium virulence and fairly rapid growth (Bov.). The second culture was isolated from a hog infected with bovine tuberculosis, was of high virulence and slow growth (S.) and was obtained through the kindness of Dr. John R. Mohler. The 27 to 29th generations were used. In order to avoid pharyngeal infection a series of animals (12 guinea-pigs, 7 rabbits, and 3 dogs) were operated upon. The tuberculous material was injected carefully with an hypodermic needle into the stomach or intestines which were sewed to the abdominal wound. In some cases a small opening was made, a capsule of the culture inserted, and the wound in stomach or intestine and abdomen closed tight. In every case it was found that the edges of the wound, however small, in the mucosa, were infected with the tubercle bacillus and the glands draining such areas became tuberculous. In the dogs the mucosa was intact but the mesenteric glands draining the portion of intestine which was operated upon, showed a localized tuberculous process. No other glands were involved. The animals were killed 30 to 35 days after operation. The guinea-pigs and rabbits showed ulcers in the mucosa, a rapid extension of the process through the mesenteric glands, local or general tuberculous peritonitis and pulmonary involvement. The culture (Bov.) was used in all these experiments.

A series of 6 dogs was starved for 4 days—then two capsules (Bov.) and one capsule (S.) were wrapped in a little gauze and pushed far down the œsophagus. They were readily swallowed with no chewing. Each capsule contained the entire growth from a single glycerine agar tube. The animals were then each given one pint of milk. They were killed at varying intervals and the duct contents examined by smears and inoculations. Because of the premature death of the inoculated animals the results are of value only in the cases of 3 dogs.

Dog. 11. Fed as described and killed in 19 hours.

The duct contents: 4 cc. injected subcutaneously in a rabbit; 2 cc. injected intraperitoneally in a rabbit; a suspension made by chopping and grinding up the mesenteric glands in salt solution injected subcutaneously in a rabbit. None of these animals developed any tuberculosis and the glands draining the injected areas appeared normal under the microscope. Smears from the dog's gastric and duodenal mucosa showed a few

tubercle bacilli, from the mucosa of ileum and cæcum many tubercle bacilli. Smears from the duct and mesenteric glands after long search were negative.

Dog 8. Fed as described and killed in 24 hours.

The duct contents: 4 cc. injected subcutaneously in a rabbit; an emulsion of the ileocæcal gland injected subcutaneously in a rabbit; an emulsion of the jejunal and mesenteric glands injected subcutaneously in a rabbit. These animals showed no tuberculous process and their glands were quite normal under the microscope. Smears from the lumina of the dog's stomach, duodenum, ileum, and cæcum all showed a good many tubercle bacilli but smears from the duct and mesenteric glands were negative.

Dog 9. Fed as described and killed in 24 hours.

The duct contents: 7 cc. injected subcutaneously in a guinea-pig; 2 cc. injected intraperitoneally in a guinea-pig. An emulsion of the mesenteric glands injected subcutaneously in a guinea-pig. These animals did not develop any tuberculous process and the microscope showed normal glands. Smears from the dog's ileum showed many tubercle bacilli but smears from the mesenteric glands and duct contents were quite negative.

Dogs 6 and 7. Fed as described and killed in 4 hours. The inoculated animals died the following week (pneumonia). Smears from stomach and duodenum showed many tubercle bacilli, but smears from glands and duct were negative after very careful search.

Three dogs were fed as described and kept as controls but died of a peculiar bronchopneumonia in 2 to 3 weeks. Autopsy showed no lesions of tuberculosis in spite of careful microscopical study of the mesenteric glands.

A series of 4 guinea-pigs (adult) was starved for three days, then to each one was fed one capsule (Bov.); the next day they were similarly fed. Each capsule contained the growth from one glycerine agar culture of the tubercle bacillus (Bov.) and was pushed far back into the pharynx. The pigs could not swallow it without chewing and soiling the mouth and pharynx.

Guinea-pig 34. Fed as described and killed 24 hours after second feeding. Emulsion of duodenal and ileocæcal glands injected subcutaneously into a guinea-pig; emulsion of large mesenteric gland injected subcutaneously into a guinea-pig. The gland fragments wrapped in gauze and planted subcutaneously in a rabbit.

The inoculated animals were killed after 60 days and showed no tuberculosis. Smears from the mucosa of stomach, ileum, and cæcum all showed many tubercle bacilli, but smears from the glands were negative.

Guinea-pig 37. Fed as described and killed 48 hours after second feeding. Emulsion of ileocæcal and duodenal glands injected subcutaneously in a guinea-pig. The large mesenteric gland planted subcutaneously in a guinea-pig. The gland fragments wrapped in gauze and planted subcutaneously in a rabbit. The inoculated animals killed in 61 days showed no tuberculosis. Smears from the ileum and cæcum showed many tubercle bacilli, but smears from the stomach and mesenteric glands were negative.

Guinea-pig 40. Fed as described and fed cabbage leaves 4 hours before killing, 72 hours after the feeding of second capsule. Emulsion and glands treated exactly as in Guinea-pig 37. The inoculated animals killed in 60 days showed no tuberculosis. Smears from ileum and cæcum showed tubercle bacilli, but smears from the stomach and mesenteric glands were negative.

Guinea-pig 43. Fed as described and fed cabbage leaves on 4th and 5th day. Killed 5 days after feeding of second capsule. The ileocæcal gland planted subcutaneously in a guinea-pig. Half a large mesenteric gland planted subcutaneously in a guinea-pig. Duodenal and half a large mesenteric gland planted subcutaneously in a rabbit. The inoculated animals killed in 58 days showed no tuberculosis. Smears from the cæcum showed tubercle bacilli, but smears from the mesenteric glands, stomach, and ileum were negative.

These four guinea-pigs who had ingested many tubercle bacilli, and were killed 1 to 5 days after such feeding showed no tubercle bacilli in the mesenteric glands, although the bacilli were present in large numbers in the intestinal lumen as shown in smears. Control guinea-pigs which were fed in a similar manner, and killed in 4 to 5 weeks showed caseation of the ileocæcal or duodenal, and mesenteric glands with only occasional small tubercles in lungs, spleen, or liver.

In reviewing these results it must be remembered that a culture of moderate, but not low, virulence was used, and that the dose was not extremely large. It would seem that under such conditions the tubercle bacilli were not swept along through the lymphatic apparatus of the intestine in a few hours, else the control animals would have shown tubercles of equal age in the lungs, spleen, etc., and mesenteric glands. The inoculation animals as well should have shown some tuberculosis, but as the mesenteric glands were free from the tubercle bacilli even as late as the fifth day after feeding, we may conclude that the process is a slowly advancing one. It is possible that by feeding animals with enormous numbers of exceedingly virulent tubercle bacilli, a few of the bacilli may be carried along the lacteals, and pass through the mesenteric glands, into the duct and blood stream, Ravenal (5), Vallée (9), Calmette (10). It seems impossible that the majority of such bacteria could escape the filter of the mesenteric glands where they would lodge, and eventually cause a tuberculous lesion as old as the other lesions—a clear index that the tubercle bacilli had passed along that channel. It seems that such experiments do not closely parallel the conditions in cases of infections in man where the doses are small, and the organism perhaps exposed to factors which tend to lower its virulence. The findings in these cases agree with the recent work on experimental pulmonary anthracosis which was claimed to be alimentary in origin (Calmette and his pupils) (6), but this has been conclusively disproved by Cohn (7) and others. No review of the literature will be attempted, but mention may be made of a paper by Kovács (8) who reviews the recent literature, and outlines the position of the two schools upholding the aspiration, or ingestion theories.

CONCLUSIONS.

The tubercle bacillus can not pass from the intestine through the lacteals, mesenteric glands, and thoracic duct into the lungs without leaving some record of such passage. A few bacilli may, under favorable conditions, be swept along this course to the lungs, but the majority surely will lodge in the glands, and in time cause a tuberculous process which can be recognized. When the mesenteric glands are not involved we may exclude the intestinal tract as the portal of entry, but the converse does not hold for the tuberculous mesenteric glands which may be secondary to some pulmonary focus that is discharging tubercle bacilli into the alimentary tract. The thoracic duct is often the distributing agent in cases

which show scattered tubercles in the viscera, and tuberculous mesenteric glands.

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A HITHERTO UNDESCRIBED DISEASE CHARACTERIZED ANATOMICALLY BY DEPOSITS OF FAT AND FATTY ACIDS IN THE INTESTINAL AND MESENTERIC LYMPHATIC TISSUES.

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The following case was characterized clinically by a gradual loss of weight and strength, stools consisting chiefly of neutral fat and fatty acids, indefinite abdominal signs, and a peculiar multiple arthritis. The diagnosis lay between neoplasm and tuberculosis of the mesenteric structures. Pathologically the lesions of interest were found in the intestines and the lymphatic tissue draining this region. The intestinal mucosa showed enlarged villi due to deposits of large masses of neutral fats and fatty acids in the lymph spaces and an infiltration of the interglandular tissue by large mononuclear and polynuclear giant cells. The submucosa in many places shows similar deposit in the enlarged lymph spaces and invasion by large mononuclear cells. The mesenteric glands in gross showed the most striking changes, but under the microscope the picture closely resembled that seen in the intestine. The glands showed the same deposits in even greater amounts, and a chronic inflammatory reaction with replacement of much of the gland tissue by fibrous scar tissue, masses of large mononuclear cells or polynuclear giant cells of the foreign-body type. The lymphatic tissue of the bronchial glands, bonemarrow, and lungs showed no abnormalities of importance. The other organs are described below, but no changes were found which seemed related to the intestinal lesions.

CLINICAL HISTORY.

(58,803), X, physician, æt. 36, single, was admitted to the Johns Hopkins Hospital on April 12, 1907, complaining of "loss of weight and strength; rheumatism; bronchitis; shortness of breath; dilated (*sic*) abdomen; tumor of abdomen."

Family history.—Unimportant. No history of tuberculosis in any branch of family.

Previous history.—Up to five years before the entry the patient had been a remarkably healthy man. Measles and whooping-cough as a child. Chills and fever at 10. Slight attack of pleurisy at 14—in bed only a day or so. In 1899, mild attack of influenza.

Has had some trouble with his nose for which a small portion of each inferior turbinate bone has been removed without benefit. Tonsils were excised when he was a child.

As long as he can remember he has had a slight hacking cough and a desire to "clear his throat." For four and a half years the patient has, he says, had a "bronchitis" with chronic cough, which has always been worse in cold and damp weather.

The patient has been working as a medical missionary in the East, mainly in Constantinople, whither he went in 1899. In his work he has frequently been thrown with tuberculous patients.

The present illness began insidiously, five and a half years ago, immediately on his arrival in Turkey. The first symptoms were attacks of arthritis coming on in various joints. They were transient, the first lasting but six or eight hours. These recurred again and again three or four times a week in damp weather, once a week perhaps, in dry weather, lasting from six to twenty-four hours; rarely severe enough to keep him from work. Nearly every joint has been affected. Sometimes the joints were hot, swollen, and tender; at other times, only painful. Again the pain might seem to be in the muscles; or with pains in the joints there were also pains along the course of both sciatic nerves. The attacks were never associated with fever and on but one occasion were they of sufficient severity to confine him to bed and for but two days. These attacks were associated with a gradual loss of weight and strength. In the course of a year he developed a cough which has continued ever since, varying, however, greatly in severity according to weather and climate—better in dry seasons and climates, worse in damp. This was associated with an expectoration of moderate quantity, of a yellowish color, tenacious and raised with difficulty—more abundant in the morning.

Although gradually losing weight and strength he kept at work, with occasional vacations, until September, 1906, when he came back to America, spending a month in the Adirondacks, where he gained five or six pounds. Thence he proceeded to Atlanta where, in the course of five or six weeks, his cough became much worse, the expectoration increased, and a slight evening fever developed, the temperature rising to about 100°. There were occasional "night sweats" and notable loss of strength and weight. Physical examination showed nothing definite.

Examination of the sputa for tubercle bacilli was negative.

In December, 1906, the patient, fearing tuberculosis, went to New Mexico, where his bronchitis improved. The loss of weight, however, continued, and a diarrhœa set in which has persisted ever since, the stools, from three to four a day on an average, of fluid or semi-solid character. Examination by the patient himself, revealed a deficiency in bile and an excess of fat.

Shortly after reaching New Mexico, three and a half months ago, the patient observed a swelling of the abdomen, which gradu-

ally increased until the circumference amounted to thirty-three inches, since when it has remained stationary. Soon after this a mass became palpable below and to the right of the umbilicus, while there was a still larger indefinite area of dulness and resistance in the same region. There has been some tenderness on pressure in this region.

About *four weeks ago* both ankles, especially the left, became hot, swollen, red, and tender and attempts to walk were painful. This condition, although somewhat improved, still persists.

For the last four or five weeks he has noticed dyspnœa on exertion. The appetite has always been good. No history of jaundice.

Blood Examinations.

April 14. Fresh blood—red cells are pale and irregular in size, there being many microcytes. No nucleated red blood cells. No myelocytes. No marked poikilocytosis.

R. B. C., 4,468,000; W. B. C., 8180; hæmoglobin, 52%.

Differential count:

Polymorphonuclears	410	80.4%
Small mononuclear lymphocytes	16	3.1%
Large mononuclear lymphocytes	32	6.2%
Eosinophiles	47	9.2%
Large mononuclear cells	2	0.4%
Mastzellen	3	0.6%
	510	

April 21. R. B. C., 4,464,000; W. B. C., 8420; Hæmoglobin, 54%.

April 29. R. B. C., 3,932,000; W. B. C., 6780; Hæmoglobin, 53%.

April 30. Coagulation time, 5 minutes 30 seconds.

May 1. Differential count:

Polymorphonuclears	491	89.3%
Small mononuclear lymphocytes	19	3.5%
Large mononuclear lymphocytes	19	3.5%
Eosinophiles	17	3.1%
Mastzellen	1	0.2%
	547	

Examination of Stools.

April 14. Stool is almost white or creamy and has a smooth silky appearance. Under the microscope one sees enormous numbers of fatty acid crystals. They appear as small needle-like crystals arranged in tufts or rosettes which do not stain with Soudan III. This stain shows an abundance of neutral fat in fine globules. Vegetable cells are present and a few pieces of striped muscle. No parasites nor eggs are seen after long search.

Several examinations for tubercle bacilli negative.

April 24. Stool is clay-colored. Microscopically it resembles the ones previously examined with perhaps some increase in neutral fat.

April 28. Stool darker colored. No bile was demonstrable. Fatty acids and neutral fat present in large amounts.

Dr. Boggs. April 20. Stool almost completely composed of split fats and soaps in crystalline form indicating interference with fat absorption. Neutral fat small in amount. Some undigested starch present. Reaction of stool is acid.

Dr. Voegtlin. April 30.

Dried stool, 20 gms. { Neutral fat, 10 gms. / Fatty acids, 6 gms. / Organic salts, etc., 4 gms.

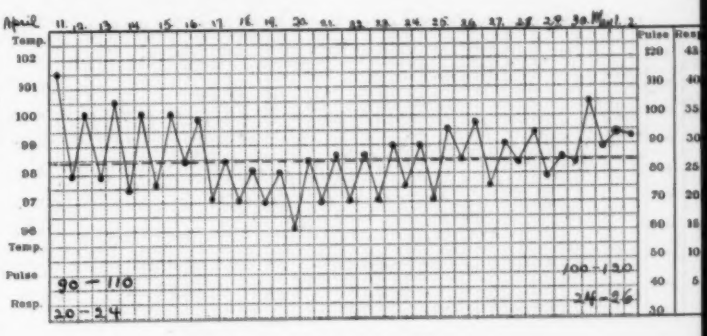
Diet.—While in the medical ward the patient was on a full diet with four raw eggs daily and eight ounces of milk every two hours. In spite of this forced feeding the patient lost weight every week, weighing 145 pounds two weeks before his death. Normal weight, 175 pounds.

Urine Examinations.

April 12. Clear, yellow color. Specific gravity, 1029; acid reaction; no sugar; no albumin; red finely-granular sediment; no casts; many uric acid crystals; diazo negative. Later examinations showed the same general picture.

April 29. Calcium oxalate crystals were present. No bile. *Urine* obtained shortly before death showed the presence of a considerable amount of *acetone* but no diacetic acid.

May 3. .001 gr. of tuberculin was given. No reaction followed. No sputum was obtained except a small amount of clear mucus showing no tubercle bacilli.



Clinical Notes.

Dr. Thayer. April 15, 1907. The patient was thin, and though sunburned was evidently pale. There remained still a good deal of tonsillar tissue with well-marked crypts.

The *thorax* was unsymmetrical, the cartilages of the fifth and sixth ribs of the left side being evidently prominent. The movements of the right upper front were rather freer than those of the left side, and on percussion there was a slight dulness with a trace of tympany in this area. On quiet respiration the inspiration was here a little wavy but no adventitious sounds were heard. Elsewhere, the respiration was clear.

Heart.—Sounds best audible in the fourth space, inside of the mammillary line, about 7.7 cm. from mid-sternal line, at which point dulness begins. Sounds, clear throughout; second pulmonic a little louder than second aortic.

The *abdomen* was rather full. Just to the left of the median line in the epigastrium there was a slight prominence which suggested a small properitoneal hernia. The abdomen was more resistant on the right than on the left, and especially in the right lower quadrant where the fulness seemed more marked; there was a "rather elastic resistance," especially below and to the right of the navel. Tympany on percussion; somewhat duller in the middle of the abdomen and in the left flank. No movable dulness.

The *liver* was not palpable, extending by percussion to a point a little above the costal margin in the mammillary line, and in the median line to a point midway between the umbilicus and xyphoid cartilage. The splenic dulness reached the costal margin but the border could not be distinctly felt.

A few small *glands* were palpable in the axillæ and the epitrochlears were both palpable.

The left *ankle* was swollen, the skin tense and shiny. On the outer side of the foot and on the dorsum there was a diffuse discoloration suggesting old cutaneous hæmorrhage. A greenish-yellow coloration extended from the toes to above the malleoli, while at points there were deeper bluish areas gradually fading into the yellow-green. The ankle was quite hot. On the legs and thighs were a few faded, brown purpuric spots no larger than a pin-head.

In the middle of the left leg, just to the left of the tibial crest,

there was a discolored, greenish, slightly indurated spot having the appearance of a fading patch of erythema nodosum. On the right leg and calf were several similar areas.

Dr. Baetjer. April 17. Radiograph of ankles does not show any bone changes. There is, however, a slight thickening of the periarticular tissues around joints. This does not seem to be tuberculous. No exostosis nor erosion of any bones.

Dr. Barker. April 19. There is a little general pigmentation. Glands in right posterior portion of neck are palpable. Chest shows expansion a trifle better on the right side. There are pigmented moles on chest. Vocal fremitus is normal. Percussion clear. A slight fraction heard in left lower back and a few fine crackles in right supraspinous region. Heart sounds clear. Abdomen full, slightly more marked on right side. Slight tenderness to right of navel. Dulness in right flank; none in left. Slight swelling of left, but more of right ankle.

Dr. Thayer. April 20. Abdomen is a little generally distended and everywhere tympanitic. Less tenderness to-day than last time. There is a muscular resistance to deep palpation in the right upper quadrant just above and to right of umbilicus. No definite mass is felt.

Dr. Baer. April 18. Both ankles are markedly swollen and pit on pressure. There is a slight amount of local temperature, no decided pain on pressure over bones. Dorsal flexion is somewhat limited. Abdomen is much distended with a decided movable mass just below umbilicus.

Dr. Thayer. April 25. Left ankle is not so swollen and looks better. Abdomen is not so swollen—a doughy resistance. Just below navel is felt a nodule the size of a walnut. Palpation here causes a little pain in left side of abdomen. Some suggestion of a lesion at left apex but nothing definite. On deep inspiration in left lower axilla in sixth and seventh interspaces there is an exceedingly soft friction rub—definite in forced inspiration and expiration. This is present also over left lower back, rather more audible than in front. An occasional fine crackle at extreme base of right lung.

Dr. Thayer. April 29. Auscultation of left apex shows a wavy interrupted inspiration but no adventitious sounds. Percussion note a little higher pitched than on right. In the left lower axilla and back a soft friction is audible, reaching to within three finger's breadths of angle of scapula. Over a small area below angle of scapula in right lower back a very rough scratchy friction is heard. Percussion note at both bases is impaired. Heart, no enlargement; sounds clear; pulmonic second sound is accentuated. Abdomen is very full with limitation of respiratory movements, walls not so resistant as before. A rather indefinite tumor felt to right of umbilicus, it is slightly tender. At times to right and above navel a tumor is felt, very movable and rather sausage-shaped.

May 5. Patient transferred to surgical wards for exploration. Operation May 6. No fluid in abdominal cavity. Mesenteric glands very much enlarged and hard. Abdomen was closed. Diagnosis, tuberculosis of mesenteric glands. Patient did well for 48 hours after the operation. He perspired quite freely at times and was troubled with joint pains but slept a good deal. He was on a liquid diet and had frequent enemata, which were not very effectual. Dyspnœa was noticed two hours before death and respirations then numbered 40 per minute; pulse 120.

Dr. Cole. May 8, 1907. The patient was seen by me at 9.30 p. m., at which time he was perfectly conscious, propped up in bed and suffering from extreme polypnœa. The distress seemed to be both with inspiration and expiration. There was only moderate cyanosis, though the skin was cold and clammy. There was no striking odor to the breath. A few râles were heard over both lower lobes, but no areas of consolidation were made out and the condition in the lungs did not seem to be sufficient to account for the extreme grade of dyspnœa. Pulse was rapid, but regular, and of fair quality. He did not seem to be in immediate danger. An attempt was made to have him void as a condition of acidosis was at once suspected and it seemed advisable to obtain some urine for examination. He was unable to void and preparations were being made to catheterize him when he suddenly died.

Clinical Discussion.—*Dr. W. S. Thayer.*

The clinical pictures of this case were in many ways remarkable. The cough, the fever, the progressive emaciation, the abdominal swelling and tenderness, the remarkable character of the stools, indicative of defective fat absorption, were decidedly suggestive of a pulmonary and mesenteric tuberculosis.

On the other hand, the physical signs did not justify a diagnosis of pulmonary tuberculosis and the sputa were negative. The signs at the left apex were interpreted clinically as evidence of an old retraction and not of an active process. Again the blood picture was distinctly not that of a tuberculosis. The anæmia was more marked than common and the eosinophilia present on entry was peculiar. In addition to this were the condition of the ankles with the remarkable history, together with the purpuric manifestations and the areas suggestive of erythema nodosum—symptoms which raised the question as to whether the case might belong to that ill-defined group which has been roughly brought together through the common manifestations of erythema multiforme exudativum and arthritis.

Further examination of the stools confirmed the existence of permanent interference with fat absorption without deficiency in fat splitting or azotorrhœa, while the absence of reaction to .001 tuberculin was strong evidence against the presence of an active tuberculous process.

These observations, together with the result of the exploratory laparotomy led to a final diagnosis of sarcoma or Hodgkins' disease of the mesenteric glands.

It is a matter of great regret to me that I was unable to see the patient after the operation. The remarkable manner of death was as Dr. Cole observed, suggestive of an acid intoxication.

As one looks back upon the history of this case in connection with the remarkable observations at autopsy, it is difficult to resist the conclusion that we are here dealing with a definite and hitherto unrecognized clinical picture with which we shall meet again.

Autopsy Protocol.

Dr. X. Aet. 36 years. Ward C, 2. Autopsy No. 2883. Died 10.40 p. m. May 8, 1907. Autopsy 2 p. m. May 9, 1907. Dr. Whipple.

Anatomical Diagnosis.—Neutral fat and fatty acid deposits in intestinal mucosa, mesenteric and retroperitoneal glands and thoracic duct; chronic lymphadenitis; anæmia; emaciation; organizing peritonitis, pleuritis, pericarditis, and aortic endocarditis; cardiac dilatation and hypertrophy with fatty degeneration; chronic passive congestion of viscera; splenic tumor; hyperplasia of bonemarrow; cloudy swelling

of viscera; laparotomy wound; bronchopneumonia and œdema of lungs; caseous apical scar and tuberculous bronchial lymphadenitis.

Body is that of a well-developed, large-framed, white male, 180 cm. in length. Rigor mortis well marked. The skin of the face and hands shows a deep brownish pigmentation (sunburn). The skin over the trunk and limbs shows no excess of pigment. Over the dorsum and lateral aspect of the left ankle and instep are several diffuse purple spots and the joints show a boggy swelling. The abdomen is slightly distended, shows a recent surgical incision about 10 cm. in length closed by silver sutures just to the right of the umbilicus. The abdomen on incision shows a slight excess of slightly turbid yellow fluid. The intestinal coils are moderately distended with fluid and gas. The loops of ileum and the cæcum are adherent by rather elastic, but easily torn adhesions to the under surface of the scar described above. The peritoneal lining everywhere has lost its gloss and is covered by grains and shreds of moist thready tissue. This exudate is quite well marked in the pelvis where the threads are quite conspicuous and cannot be separated from the intestinal coat without considerable force. The same milky adhesions are present over the spleen and liver. The appendix is clear.

Thorax shows both pleural cavities to be invaded by this same type of inflammation. The cavities contain a little excess of fluid and the serous surfaces are frosted over by these rather elastic moss-like gray adhesions which are most conspicuous over the diaphragmatic surfaces and the posterior portion of the lower lobes. The fat in the region of the mediastinum shows numerous ecchymoses. The pericardial cavity is everywhere obliterated by elastic gelatinous-looking adhesions, in which new-formed blood-vessels can be seen with great distinctness. No fresh fibrin is found anywhere. The two layers can be separated with some difficulty, showing ecchymoses here and there.

Heart, together with the pericardium, weighs 680 gms. It is dilated and hypertrophied. The right auricle shows some dilatation with firm pale gray clots. The tip of the auricle is clear. The tricuspid valve measures 15 cm. in circumference. The valve leaflets are delicate. The pulmonary valve is normal. The intima of the right heart is thin and smooth, through which one sees well-marked mottling of the muscle columns with yellow flecks. The left auricle is moderately dilated, its intima smooth. The mitral valve measures 12 cm. in circumference, and is delicate. The aortic ring measures 8 cm. in circumference. Two of the cusps are normal. The third cusp situated posteriorly and just above the anterior curtain of the mitral valve shows a small sessile vegetation 6 mm. in long diameter, situated on the line of closure close to the Corpus Arantii. It is of an opaque yellow color on its upper portions, but its base shows invasions by delicate capillaries growing up from the base of the valve. The intima of the left heart is smooth and the muscle shows through it, of a brownish color, mottled with yellowish flecks. The coronary vessels show a few patches of sclerosis. The heart muscle is pale and flabby and of a mottled yellowish-brown color on tangential section. The wall of the left ventricle averages 13 to 15 mm. in thickness.

Lungs.—The left lung is voluminous. The vessels and bronchi at the hilum are clear. The pleural surface shows the adhesions described above, some of which are invaded by delicate capillaries. On section the lung tissue is everywhere very moist and exudes a frothy serous material. It is of a yellowish-red tint in the upper lobe, becoming deeper red in the lower lobe. Here and there one sees a few slightly raised purplish areas of irregular size and extent, which are rather dryer than the surrounding tissue and just palpable. At the bifurcation of the main bronchus one finds a calcified lymph-gland, measuring 2 cm. in long diameter. In the apex of the upper lobe is found a small calcified nodule 3 to 4 mm. in diameter, above which the pleura shows fibrous tags. Further examination of this scarred apical portion shows two or three other small foci of cheesy material, none of them exceeding 5 mm. in diameter. The *right* lung shows a condition in general resembling the left. There are numerous subserous hæmorrhages over the lower lobe. Cut section resembles the other lung. It is very moist. The right lung is even more voluminous than the left.

Spleen weighs 375 gms., measures 18 by 9 by 4 cm. It is adherent by old adhesions to the diaphragm. Its capsule shows numerous irregular milky areas of thickening. On section the Malpighian bodies appear very conspicuously as large indefinite milky dots, 1 to 1½ mm. in diameter. The spleen pulp is of a brick-red color, and scrapes off with ease on the knife. The trabeculæ are easily seen. The organ is flabby and flattens out on the table.

Stomach is greatly distended with sour-smelling clotted material. Its mucosa shows considerable postmortem digestion and occasional ecchymoses. The duodenum shows a velvety mucosa, stained with bile. The bile papilla is normal. The bile and pancreatic ducts open side by side, they are delicate and normal everywhere.

Pancreas is rather large and pale. Consistency is about normal. Cut section shows a pale watery-gray parenchyma, on which one sees distinctly minute opacities of pin-point size. The stroma does not seem to be increased in amount, but is quite loose and œdematous.

Liver weighs 2570 gms., measures 29 by 24 by 9 cm. Its upper surface is covered over by moss-like elastic adhesions, some of which show invasion with blood-vessels. The lower surface shows a similar, but less extensive peritonitis. Cut section is everywhere quite uniform and pale. The lobulation is distinct, the lobules being rather swollen, with a pale-red center and a more opaque-gray periphery. Here and there are seen a few minute areas of yellowish opacity, one of which looks like a small tubercle. Consistency is about normal.

Kidneys weigh 420 gms. The left kidney measures 13 by 6 by 3½ cm. The capsule comes off easily, leaving a pale smooth surface, showing occasional retention cysts. Cut section shows a pale-gray cortex, averaging 6 to 7 mm. in thickness. The striations are perfectly regular. The majority of the glomeruli appear as minute red dots. The tubular portion of the cortex is swollen and gray. The pyramids are normal. The pelvis is normal. The right kidney resembles the left.

Adrenals are of normal size. On section show an opaque-yellow cortex, 1 mm. in diameter, and a thin brown medulla.

Thyroid appears normal; the neck organs could not be removed.

Aorta shows a few small patches of yellowish thickening. It retains its elasticity well.

Bladder shows a pale smooth mucosa.

Rectum normal.

Prostate, *seminal vesicles*, and *testicles* normal.

Marrow of femur is of a mottled yellowish-pink color and rather firm.

Intestine.—The jejunum is dilated, shows a pink or red velvety swollen mucosa, which is flecked over thickly with little pin-point yellowish grains, which seem to be intimately connected with the mucosa, even in some cases beneath it. No ulcerations are seen. The lower portion of the jejunum shows a rather paler mucosa of the same description, and everywhere thickly dotted over with these little yellowish-white grains. The Peyer's patches in the ileum are not conspicuous. The large intestine shows a pale smooth mucosa.

Mesenteric glands present a most remarkable appearance. They are greatly enlarged, some of them measuring 3 to 4 cm. in long diameter. They are rather elastic to the touch. There are many small glands close to the mesenteric attachment, about ½

cm. in diameter. On section the smaller glands are found to be of an opaque pale-yellowish color, with almost complete disappearance of the gland tissue. There is an indefinite translucent reticulum, through which one sees minute grains of opaque yellow color. These are thickly sown throughout all the glands, and in some instances seem to be located in cyst-like pockets, from which these little grains can be scraped out on the edge of the knife. Some of the larger glands present considerable injection and show some small hæmorrhages into this translucent stroma, which everywhere is dotted over with these little grains of yellowish color. The glands on section bulge beyond the capsules. A similar condition is seen in the glands at the root of the mesentery in the neighborhood of the pancreas. Some of the glands here measure 2 cm. in long diameter. Some of them are quite opaque and yellow. They seem to be full of little cystic areas, some of which contain a viscid fluid, others little yellow grains. The retroperitoneal lymph-glands about the cœliac axis show exactly the same picture.

Thoracic duct is dissected out. Smears made from its content and stained show no bacteria but many mononuclear leucocytes and large mastzellen. The fluid from the thoracic duct shows numerous small highly refractile droplets and small rosettes of pale greenish acicular crystals often attached to the side of a fat droplet.

Scrapings from the cut section of the mesenteric glands under the microscope show typical tufts and balls of delicate spindle-shaped crystals. These crystals dissolve with a slight amount of heat and are reformed on cooling. They come down in little star-like masses of needle crystals, which are much smaller than the original crystals. The crystals dissolve easily in alcohol and ether, and are evidently fatty acid. Similar crystals are found in the scrapings from the intestinal mucosa. Fresh cut section of the glands shows a neutral reaction to litmus. No bacteria are made out in smears. One of the small mesenteric lymph-glands is inoculated subcutaneously into a rabbit; animal died in seven weeks; negative for tuberculosis.

Microscopical Preparations.

Tissues hardened in Zenkers fluid, formalin, or alcohol. The routine stain was hæmatoxylin and eosin.

Heart.—The pericardial cavity is almost entirely replaced by a loose œdematous granulation tissue of connective tissue and wandering cells in which blood-vessels are quite conspicuous. There are numerous chinks in this granulation tissue which are lined by cubical epithelium derived evidently from that of the pericardial cavity. In some small areas there is an exudate of polymorphonuclear leucocytes, red blood-cells, and fibrin. The heart muscle-cells are of about normal size but show a moderate grade of fragmentation. The aortic valve shows a dense hyaline mass of old fibrin which is being invaded by fibroblasts, wandering cells, and blood-vessels.

Lungs.—The pleura is thickened and infiltrated with many wandering cells and new-formed blood-vessels. There are numerous adhesions consisting of scar tissue or organizing granulation tissue. Beneath the pleura many of the alveoli show an exudate of red blood-cells and heart-failure cells mixed in with a fine pink granular coagulum. Other alveoli show a hyaline-like exudate of fibrin which is being invaded by wandering cells, fibroblasts, and capillaries. In such areas the alveolar walls are greatly thickened, consisting mainly of a thick mass of young fibroblasts and blood-vessels. The alveolar epithelium here is cubical and beneath it are many phagocytes full of coarsely granular yellow pigment. In all sections of lung tissue the alveoli show some coagulated serous material and numerous heart-failure cells. In some areas the alveoli show a fresh exudate of fibrin, red blood-cells, and leucocytes. The bronchi in some instances show a similar exudate and the epithelium is well preserved. The capillaries are congested and the larger blood-vessels are normal. The lymphatic tissue of the lung is normal in amount and character. Coal pigment is present in moderate amount.

Spleen.—The capsule is thickened and shows signs of a chronic inflammatory process. The trabeculæ are thickened but widely separated from each other by an increase in spleen pulp. The blood-vessels show some thickening of their walls and in some instances a hyaline degeneration of the subintimal tissue. The Malpighian bodies are enlarged, but as a rule show no abnormalities. Some of them show an increase of stroma with disappearance of lymphoid-cells in the immediate neighborhood of the central arteriole and others show many polymorphonuclear leucocytes in their peripheral zone. The venules of the spleen pulp are full of blood and their walls are somewhat thickened, showing evidences of some chronic passive congestion. The pulp-cells are increased in number, between which are seen numerous cells of polyblastic type (Maximow), red blood-cells, and leucocytes. The stroma of the pulp is definitely thickened and easily made out. Numerous accumulations of coarsely granular yellow pigment are found in the pulp, often some of the smaller grains being included in large phagocytes.

Marrow of femur.—There is considerable increase in the cellular elements, but the fat-cells are quite in evidence making up more than half of any section and appear quite normal. The giant cells and myelocytes occur in normal proportion. The eosinophile cells are not increased in number. Red blood-cells are not conspicuous, but the nucleated reds are quite numerous and definitely increased in number. They occur in clumps of 3 to 20, which are scattered thickly throughout the sections. The same yellow pigment as described in the spleen is present in all parts of the cellular marrow and is often included in large phagocytes. The lymphatic tissue of the spleen and marrow shows none of the remarkable changes found in that of the mesentery and intestine, but the changes here are dependent on a secondary anæmia.

Blood-clots. Sections show no change of importance.

Liver.—The capsule is thickened and shows many adhesions made up of scar tissue and blood-vessels. The stroma at the margins of the lobules is increased in amount and invaded by many polymorphonuclear leucocytes which are present as well in the capillaries of the lobules. This change is most marked just beneath the capsule and seems to have a direct relation to the extensive perihepatitis. The capillaries in the central portion of the lobules are dilated with a corresponding atrophy of the liver cells which here contain fine yellow pigment. The liver cells at the margin of lobules are swollen, and granular, some of them showing small fat vacuoles. The bile-ducts are perfectly normal.

Adrenals.—Its cortical cells are regularly arranged and of the usual appearance. Many of them show fat vacuoles. The medulla is inconspicuous. The perirenal fat is quite normal in appearance.

Kidneys.—The cortex shows a regular architecture, but there is a slight diffuse increase in connective tissue between the tubules. The glomeruli are of normal size, but many show some thickening of their capsules. The convoluted tubules show a swollen pink-staining granular epithelium which shows the "brush border" quite well and whose nuclei stain sharply. Their lumina are slightly dilated and contain foamy or granular-looking débris but no casts and no exudate of cells. The pyramids show normal tubules which contain no casts, but the interstitial stroma is quite œdematous. Blood-vessels are normal and the capillaries contain little blood.

Pancreas.—Sections from various parts of the organ show no changes of importance. The islands of Langerhans are rather large, sharply outlined by a thin capsule, and made up of normal-

looking cells, a few of which show mitotic figures. The acini in many places show postmortem changes, but elsewhere are normal, as are the pancreatic ducts. The interlobular stroma is loose, its meshes being separated by a pink granular coagulum in which can be made out a few mononuclear wandering cells. The fat-cells in this stroma are normal. The interacinar stroma is very delicate.

Skin and subcutaneous tissue from abdomen is quite normal. The fat-cells are sharply contoured.

Thyroid.—Its acini are regularly arranged and contain normal colloid. The interacinar stroma is loose and œdematous, showing as well some pale-staining colloid material.

Jejunum and ileum.—Sections made from various levels in the small intestine all show the same general picture.

Frozen sections stained lightly with osmic acid and Soudan III, show deposits of fat in the villi and submucosa. Fatty acid crystals are not stained and show up very clearly as rosettes of needles which are intimately associated with the neutral fat (compare Fig. 1) and make a beautiful contrast. Tissue hardened in formalin and stained by the Marchi method (1) shows the presence of large masses which reduce the osmic acid and are called fat droplets for the sake of brevity. The fat in the tissue at the mesenteric attachment stains as usual, appearing as large oval or circular, sharply and evenly contoured masses of a uniform jet black. Large black masses are seen in the interglandular tissue of the mucosa and in the submucosa (Fig. 2). These are not evenly contoured, but show nodular or even serrated margins and all manner of shapes. They do not stain uniformly and one may see the center or any portion of a large mass which has a feathery or fern-like appearance, due evidently, to the presence of the crystals of fatty acid. In some instances the outlines of typical rosettes are preserved in the Marchi preparations of the intestine, but this finding is common in the gland tissue. The crystals reduce the osmic acid, but they are not as black and opaque as the fat droplets. The majority of the black masses fill the spaces in which they lie but some only partly do so, the rest of the space being filled with a fine reticulum of coagulum suggesting lymph. Some of these spaces in the villi contain a fine spider-web-like reticulum of coagulated material in which may be embedded a few mononuclear cells or a small droplet of fat (Fig. 8). A lining endothelium can often be made out in such cases, suggesting that these are dilated lymph radicles perhaps occluded by a fat embolus located proximally. One may see droplets of varying size, many of which do not exceed twice the diameter of a lymphocyte, and they may be so closely packed that it seems sure that there is a deposit of this fatty substance *outside* of the lymphatics as well as in their lumina. The epithelial cells lining the crypts of Lieberkühn show no fat droplets, but there are many goblet cells with accumulations of mucus. They are quite normal in appearance. The interglandular stroma shows but few very fine grains of fat such as one finds in its venules in the circulating white corpuscles. A few of the large mononuclear cells of the plasma-cell type show these fine black grains, but the peculiar cells which are distinctly abnormal in this location do not show any fat grains, or at the most only a few. These cells have a vesicular nucleus and a pink-staining, frothy-looking protoplasm. With ordinary stains the cells seem to be packed with fine fat vacuoles of nearly uniform size, but these do not stain with osmic acid. The polynuclear giant cells are not numerous and show only occasional fat grains. The solitary follicles show no large accumulations of fat, but they are invaded by numbers of the large mononuclear cells. Some of the plasma cells here show a few grains of fat. The muscularis mucosæ is quite thickly sprinkled with fine black grains, which seem to be both intra- and extra-cellular. The capillaries and venules in this neighborhood often show some fatty grains in the endothelial cells.

Sections stained with hæmatoxylin and eosin show the very conspicuous vacuoles (Fig. 3), many of which contain a finely granular, pink-staining reticulum. Some of these vacuoles are lined by endothelial cells, giant polynuclear cells, numbers of the large mononuclear "foamy" cells, or a combination of any or all of them (Fig. 3). Other vacuoles are surrounded by a thin capsule of quite dense fibrous tissue in which are embedded many or few of the wandering cells. The interglandular tissue is made up of numbers of lymphocytes, plasma cells, and eosinophiles in about the normal number, plus the unusual mononuclear cells (Fig. 4). There seem to be two kinds of large mononuclear cells or very different types of the same cell. One resembles exactly the "polyblast" of Maximow (2) and is not very numerous here. Its protoplasm stains a deep pink and is finely granular, while its nucleus is vesicular, but shows well-marked strands and grains of chromatin. The majority of the giant cells appear to be formed by a fusion of such cells and show the same type of nucleus and protoplasm. The second type of cell has a pale vesicular nucleus, which is poor in chromatin, 5 to 7 μ in diameter and often eccentrically situated. Its protoplasm is abundant and has a foamy appearance, due to the presence of closely-placed vacuoles or granules which are often quite uniform in size, but may vary from 5 μ down to the size of an eosinophile granule. Some of the granules seem refractile and suggest mastzellen, but stains for these cells (1) show the same "foamy" protoplasm with non-staining vacuoles. Mastzellen are present in considerable numbers.

The "foamy" cells average 20 to 30 μ in diameter but show evidence of active motility and are of every conceivable form. Mitoses are seen in these cells very rarely. They are occasionally phagocytic to red blood-cells, old blood pigment or nuclear fragments. A few cells are seen which may be transition forms between them and the common polyblast, showing a vesicular nucleus and finely granular pink protoplasm, in which are a few of the vacuoles described in the "foamy" cells.

Maximow (2) describes cells ("eiterphagocyten") which in some points resemble these "foamy" cells, but his cells contain granules which stain by various methods. Such cells he considers to be derived from the mononuclear lymphocytes of the blood, as is true of the polyblasts. The "foamy" cells form giant cells either by fusion or nuclear division, the protoplasm retaining its peculiar appearance (Fig. 4). Some nuclei show signs of degeneration, but this is unusual, and the activity of the cells speaks against their being types of degenerating polyblasts.

They are most numerous in the tips of the villi and about the fat deposits where they often make up the entire field, with almost complete absence of the lymphocytes and plasma cells. As a result of all this invasion of foreign cells and fat deposits the villi are greatly increased (more than double) in length and diameter. Their capillaries are dilated, and the connective tissue is increased in amount. There is evidence of an occasional old or recent extravasation of red blood-cells into the villi, where one may see a few phagocytes packed with yellow granular pigment. Well-preserved red blood-cells may be seen free in the tissue round the bases of the crypts. A few polymorphonuclear leucocytes are seen in these areas. The solitary follicles are but slightly enlarged and the prevailing cell is the lymphocyte. Some are invaded by numbers of the "foamy" mononuclear cells but no very striking changes are seen.

The muscularis mucosæ shows hypertrophy. The *submucosa* in some places is almost normal, but as a rule is much thickened, its vessels dilated and thickened, and the stroma filled with wandering cells. The predominant mononuclear cell is the polyblast and they often contain fine grains of fat (Marchi). Many of the "foamy" mononuclears are present, usually in the loose stroma just below the muscularis mucosæ and in the neighborhood of fat deposits. The fat droplets in some places are so

closely placed as to suggest subcutaneous fat, but close inspection shows that they are of irregular size and shape. Their margins are often outlined by giant and mononuclear cells (Fig. 3) and they are separated from each other only by a delicate granulation tissue of fibroblasts, capillaries, and wandering cells. Again, the tissue will be dense and fibrous, containing only a few fat droplets and wandering cells. Numbers of extravasated red blood-cells are seen in the submucosa, often in large clumps, but usually diffusely scattered. Yellow granular blood pigment is frequently seen included in phagocytes and is most abundant in those areas where the fat deposits are most numerous. Large eosinophile mononuclears are quite numerous in all parts of the submucosa. Careful search with oil immersion lens in sections stained by various methods failed to reveal any bacteria or parasites which could have any relation to the lesion. The muscle coats and the ganglia of the plexuses are normal. The ganglion cells show some fine fat grains in their protoplasm. The serous coat shows an organizing granulation tissue of wandering cells, capillaries, etc., of the usual type.

Glands.

Unstained frozen sections show refractile fat globules and great numbers of long acicular fatty acid crystals arranged in sheaves and rosettes. Stained lightly with osmic acid such sections give a picture represented in Fig. 1, which shows well the large and small droplets thickly sown through the gland tissue and a rosette of crystals. Marchi preparations show even more extensive fatty deposits (Fig. 5) than were seen in the intestine. The gland deposits are larger, even more irregular and closely packed, but in general closely resemble those described above. In places the fat is deposited in threads which are twisted, beaded, and packed together, resembling a reconstruction of the glomerular capillaries. Such deposits are often seen in a follicle and no endothelial cells can be made out in relation to them. Giant cells are numerous and closely applied to the margins of these fat deposits, often in little lacunæ as though they were ingesting and eroding its substance. These cells may show a fine granular protoplasm and a few fat droplets; other giant cells in the stroma may show clumps of small fat droplets in their protoplasm which may have the "foamy" appearance. Some of the giant and mononuclear cells with the foamy protoplasm show minute comma-shaped black deposits which often outline one segment of a vacuole in the protoplasm, others are rod-shaped, again beaded like small filaments of chromatin, but always in the protoplasm. Often they are associated with definite grains of jet black fat deposits in the protoplasm and for this reason are thought to be some form of fat. The wandering mononuclear cells show varying amounts of fat deposits, some only a few minute grains, others large clumps of large and small droplets, and some are so crowded with fat droplets that the protoplasm and nucleus may be almost obscured. Cells with the foamy protoplasm seem less actively phagocytic toward the fat, and great numbers of them are entirely free from it. Just beneath the thickened capsules of some of the larger glands is seen a fine cloud of minute fat droplets (Fig. 5) which are very thickly packed all through the rather œdematous stroma. Some of these grains are intra-cellular, but many are surely extra-cellular. In such areas the large foamy mononuclears may be very numerous and yet show almost no phagocytosis of fat. It is possible that this material has recently reached the cortex of the gland from the afferent lymphatics. Some of the larger lymphatics at the hila of glands (efferent) are filled with a fine granular coagulum of albuminous material in which may be seen scattered small fat granules. The fat cells of the mesenteric tissues adjacent to the gland capsule are sharply contoured by thin cell membranes and look entirely normal except for some infiltration of the intercellular tissue by small round cells, chiefly lymphocytes and plasma cells. Sections of various glands stained with hæmatoxylin and eosin show how extensive is the change in the larger glands. The tissue is honey-combed with the fat vacuoles and much of the cellular structure is replaced by dense fibrous tissue which is poor in cells (Fig. 6). It takes a deep blue stain with Mallory's connective-tissue stain. The capsule and trabeculæ are thickened and the blood-vessels dilated and increased in number.

Some of the small glands which are slightly involved show almost normal lymphatic follicles and cords, but the peripheral lymphatic sinus may be greatly dilated by an exudate of red blood-cells, mononuclear wandering cells, a few polymorphonuclear leucocytes and lymphocytes, mixed with a finely granular pink coagulum. There are small irregular fat deposits which usually first appear in the medulla of the gland between the intact lymph-cords. They are outlined roughly by collections of giant and mononuclear cells, but endothelial cells are rarely made out. The adjacent tissue is at once invaded by numbers of large mononuclear cells, eosinophiles, young fibroblasts, and capillaries forming a loose cellular granular tissue about the deposits. It is quite possible that this cellular reaction may preceed the fat deposits. This granulation tissue gradually becomes dense and fibrous causing the great distortion of the gland architecture seen in several of the photographs (Figs. 6 and 7). Free red blood-cells are present in great numbers in both large and small glands, but the ecchymoses are more striking in the older glands. Phagocytosis of red cells by polyblasts is present, but not conspicuous, and is relatively infrequent when we consider the number of both types of cells. Changed blood-pigment included in phagocytes or chinks of the stroma is hard to find except in the larger glands. In some of the small glands the eosinophile cells are very definitely increased in number, mononuclears predominating, and suggest the presence of some parasite.

A small gland which was preserved in 15 per cent formalin and stained by the Levaditi method, showed some very peculiar structures. Studied with 1/12 objective these sections show great numbers of a rod-shaped organism (?) which, with this stain, is about the diameter of the spirochæte of syphilis but not of spiral shape and rarely exceeding 2 μ in length. The majority of these structures closely resemble in form the tubercle bacillus. They are very sharply contoured and appear as jet black rods, sometimes bent but more often straight or only slightly curved. Some show a slight swelling of one end and others a beaded appearance. They are most numerous in the vacuoles, which are not completely filled with fat and contain a filmy granular reticulum (Fig. 9). The structures are most numerous at the edge of the vacuoles, where the "foamy" cells are in evidence, and are contained in great numbers in these cells. When a cell contains very many of these structures they seem to clump together and lose their sharp outline as though damaged by the process of ingestion. These structures are present at the edge of the fat droplets in less numbers and become less numerous in the adjacent tissue. Careful search made in corresponding sections stained by various aniline dyes reveals no corresponding structures. If we compare them with the various spirochætes which take this stain we, perhaps, may imagine that we are dealing with some organism which resists the common stains but reduces the silver salts, effecting considerable increase in its size. Whether this is the active agent in this peculiar pathological complex cannot be determined from the study of this single case, but its distribution in the glands is very suggestive. No tissue from the intestines nor viscera was available for the Levaditi stain and all the smears from the thoracic duct and glands were used before the study of the glands by the silver method revealed these peculiar bodies.

The vacuoles do not all contain fat deposits, some of them (Fig. 8) showing only a delicate tracery of granular pink coagulum. In such spaces there may be a few degenerated cells or

small fat droplets or the coagulum may show an exact mould of a rosette of fat crystals which have been dissolved. Some of the smaller glands have a very œdematous stroma, and all the cellular elements are widely separated. Here the large mononuclear cells show many degeneration forms in which the protoplasm is full of very large irregular vacuoles and the nucleus very faint or even non-staining. In all sections many areas are found where there are large accumulations of the large foamy or granular mononuclears and here the degeneration forms are often conspicuous. Mastzellen are present in all sections, but not numerous. One large giant cell with pink granular protoplasm is seen in mitosis, the chromatin threads being very coarse and arranged as though the division was to result in three or four cells.

Briefly the microscopical findings in the intestinal and mesenteric lesions may be summarized as follows: The villi of the small intestine are enlarged, the submucosa thickened, and the mesenteric glands enormously enlarged by deposits of osmic acid reducing bodies (neutral fats and fatty acids). Such deposits are most numerous in the glands, but alike in all these situations. They are of all sizes from minute grains intra- or extra-cellular in location, up to huge irregular droplets and there is the greatest variety of forms (Fig. 2 and 5). Many of the larger masses show rosettes of fatty acid crystals (Fig. 1) and they may occupy spaces which are lined by endothelium suggesting dilated lymph channels (Figs. 6 and 7). The majority of the larger deposits are outlined by polynuclear giant cells or large mononuclear cells of polyblastic type which in some instances seem to be eroding the fatty material and are closely applied to its edge. (Fig. 8). The epithelium of the *mucosa* is normal as far as the microscope shows. The interglandular stroma contains about the usual number of lymphocytes, plasma cells, and eosinophiles, but there is an infiltration with great numbers of polyblasts—large mononuclear, ameboid cells with pink granular protoplasm. A second type of cell which is very conspicuous has an abundant foamy protoplasm, a pale vesicular nucleus and is actively ameboid; this may be a type of polyblast. Ecchymoses are numerous wherever we find the fatty deposits. The *submucosa* shows invasion with great numbers of these polyblastic cells especially about the fat deposits which in some places are abundant (Fig. 2); in others absent. There may be a very definite eosinophilia in such areas. The *glands* show the most extensive changes, especially the larger ones (Fig. 6-7). In some the lymphatic nodules and cords are quite intact, the process seeming to begin in the sinuses of the glands with invasion of the characteristic cells and small irregular fat deposits. The next stage is an invasion by fibroblasts and capillaries with more or less extravasation of blood, increase in size and number of the fat deposits and distortion of the gland architecture (Fig. 8). The large mononuclear cells increase rapidly in numbers and giant cells become conspicuous. The final stage shows a very large gland packed with fat deposits of all sizes and shapes, whose stroma is made up of dense fibrous tissue full of ecchymoses and great numbers of giant and mononuclear cells (Fig. 6-7). Gland tissue treated by the Levaditi method shows great numbers of a peculiar rod-shaped organism (?) which does not stain by the aniline dyes and is most numerous in the vacuoles and in the neighborhood of the peculiar "foamy" cells which often include these structures (Fig. 9). Whether this is the etiological factor in this disease can not be determined from this case.

BACTERIOLOGY.

A bacillus belonging to the colon group was isolated from the mesenteric glands. Cultures from the parenchymatous organs showed a white coccus of low virulence.

A small gland was planted subcutaneously in a large gray rabbit. The animal died of pneumonia seven weeks after the inoculation. Autopsy showed a small subcutaneous abscess full of soft yellow pus. The glands draining this area were only slightly enlarged. Microscopical sections show an abscess wall of granulation tissue containing many large mononuclear phagocytes closely resembling those described in the human tissue. The central part shows necrosis. Gland-tissue from the axillæ shows merely a moderate grade of chronic inflammation and there is no evidence of tuberculosis.

CHEMISTRY.

The microscopical picture was so suggestive of an abnormal fat or a mixture of fats, fatty acids, and perhaps some toxic substance which resisted absorption by the surrounding granulation tissue that a chemical study of the glandular tissue was attempted. The small amount of available material did not permit of extended chemical investigation, but the following facts are clearly brought out. 1. The ratio of fat to fatty acid. 2. The saponification value. 3. Several negative qualitative tests.

Liver, spleen, kidney, and small intestine.—About 10 to 15 gms. of each organ were ground up in about 50 cc. of 95 per cent alcohol and allowed to stand in bottles for several days. The tissues were extracted and tested for fatty acid which was found to be present in traces in the first three tissues, and to a greater degree in the intestine. Neutral fat was present in all, apparently in normal amount.

Mesenteric glands.—About 3 gms. of material (a single large gland) preserved in 95 per cent alcohol was extracted in the Soxhlet apparatus for six hours, the alcoholic and ether extracts united and evaporated to an oily residue. Glycerine was tested for and shown to be absent. The oily residue was made alkaline and the fat removed by repeated extractions with ether. The alkaline solution showed a typical soapy appearance. This was shown to contain a soap by the following reactions: 1. One portion acidified with hydrochloric acid gave a precipitate which was soluble in alcohol. 2. A second portion treated with calcium chloride gave a typical precipitate of calcium soap which was insoluble in alcohol. The solution was made acid and the fatty acid removed with ether. The ether was evaporated and the residue weighed. The neutral fat extracted by this method weighed 0.75 gms. and the fatty acid 0.07 gms., giving a ratio of 10 to 1.

A second determination was made by another method. Four medium-sized glands weighing about 4 gms. were cut open and preserved for three weeks in about 50 cc. of 80 per cent alcohol. This alcohol was filtered off and evaporated over the water bath to a dark brown oily residue—1st fraction. The glands were then ground up thoroughly with sand and absolute alcohol and the alcohol filtered off. The residue of tissue macerated with the sand was extracted in the Soxhlet apparatus for 24 hours with ether and the ether and alcohol extracts combined. This

was evaporated on the water bath to a white waxy material—2d fraction. The glands were further extracted in the Soxhlet for a second 24 hours, but this ether extract on evaporation gave only a trace of fatty material—3d fraction.

Material from the 1st fraction (0.1116 gms.) was dissolved in neutral 80 per cent alcohol and titrated against a known solution of alcoholic potash (7.8873 gms. per liter). It required 1.05 cc. of the alcoholic potash solution to neutralize the free acid. Then 8 cc. of the alcoholic potash were added and the solution heated over a water bath with return condenser for one hour to saponify the neutral fat. At the end of this time the solution was a deep cherry red showing an excess of alkali was still present. It was found that 2.58 cc. of the alcoholic potash had been used up by the fatty acids which were set free in the saponification. This gives an approximate ratio of 5 to 2 for the fats and fatty acids in the 1st fraction. Material taken from the 2d fraction (0.198 gms.) was treated in an identical manner. This solution required but 0.35 cc. of alcoholic potash to neutralize the free fatty acid, but 3.69 cc. were used up during the saponification. This fraction showed a much higher percentage of neutral fat, the ratio to fatty acid being roughly 10 to 1. The saponification number of this material from the 2d fraction as determined by Dr. Loevenhart was 144.4. When the weights of the 1st and 2d fractions were combined the ratio of fats to fatty acids was found to be about 85 to 15 per cent—1.552 gms. fat and 0.234 gms. fatty acid extracted from all the tissue. Tests for bile pigments were negative. Tests for phosphorous were made as follows and shown to be negative. Material from the 1st and 2d fractions boiled 5 to 10 minutes with potash, then acidified with nitric acid and an equal amount of ammonium molybdate added. On boiling this solution no yellow precipitate was obtained, but the addition of one drop of an acid sodium phosphate solution gave the yellow precipitate in abundance. This test excludes the presence of lecithin in any appreciable amount. The 1st fraction showed many crystals of various types. Some of these were needles of fatty acid and others chlorides or phosphates. No crystals of cholesterine were seen. The 3d fraction showed a few tufts of beautiful slender acicular fatty acid crystals.

It is unfortunate that the tissue was not sufficiently fresh to test for enzyme action (lipase), but the following facts are suggestive. Fatty acids (0.23 gms.) were present in these abnormal mesenteric glands and presumably the majority of them were derived from high melting point fats because the well-formed crystals were present in large numbers even with a room temperature of 32 C. Neutral fats were present (1.55 gms.) and showed a low saponification number (144.4) which indicates either some abnormality of the fat or the presence of some non-saponifiable substance mixed with it. Lecithin and cholesterine were suspected but shown to be absent. In the determination of the saponification number no allowance was made for the included fatty acid (10 per cent) which would tend to raise rather than lower the number, making the contrast with normal fats somewhat less striking but would in all probability leave it abnormally low. The saponification numbers of the common fats are tripalmitin = 208.8, tristerin = 189.1, triolein = 190.4, horse fat = 199.4, hog fat = 195.6.

Discussion.

Many features of this case were of great interest but it seems that in the light of our present knowledge a lengthy discussion would be of little value. The finding of acetone in the urine shortly before death and the extreme air hunger at this time suggested some acidosis which may have been dependent on the disturbance in fat metabolism. However the acetone could be accounted for by the starvation of the tissues following the obstruction of the mesenteric lymphatics and we know that in spite of heavy feeding the patient was steadily losing weight. The large amount of unsplit fat in the stools (one-half by weight) may be explained by the incomplete action of the lipolytic ferment owing to lack of absorption of its split products. Again there may have been some lack of lipase in the pancreatic secretion, but the normal appearance of the gland is opposed to this view. The deposits of neutral fat and fatty acids in the tissues may indicate some disturbance in the synthesis of fat which Loevenhart (3) and others (4, 5) have shown to be effected by lipase. Several facts indicate that this fat is in itself in some way abnormal or that it holds in suspension some abnormal or toxic substance. 1. The saponification number is very low. 2. The fat causes a tissue reaction resembling the reaction due to an inert foreign-body. 3. The peculiar wandering and phagocytic mononuclear cells. 4. The presence of many minute ecchymoses and changed blood pigment suggests some toxin capable of effecting the solution of the capillary walls. The pathological changes are limited to the apparatus which has to do with the absorption of fats while the lymphatic tissue of the marrow, spleen, bronchial glands, etc., is relatively normal except for the changes consecutive upon a rapidly advancing secondary anæmia, resembling that seen in cancer cachexia. All this suggests very strongly that here we are dealing with some obscure disease of fat metabolism.

The disease is of some duration as evidenced by the extreme changes in some of the larger glands which show dense scar tissue and cellular reaction which must be of months' standing. From a comparison with the intestinal lesions it would seem probable that the earliest changes took place in the glands rather than in the mucosa where the dense scar tissue is much less in evidence although in general the picture is the same. Examination of the contents of the thoracic duct excludes the possibility of any occlusion of its radicles between the glands and receptaculum. The presence of fatty acid crystals in its contents must be explained by the escape of such material from the glands and the same explanation holds for the mastzellen. The presence of many eosinophile cells in the smaller glands probably accounts for the same type of cell found clinically in the blood, but no clear explanation has been found for this reaction.

The presence of peculiar structures in the Levaditi sections which do not stain by the aniline dyes, suggests a possible relation to the group of spirochætes. It is not claimed that this is the etiological factor in this disease but its distribution in the glands is very suggestive. It is always found in the peculiar vacuoles and cellular granulation tissue which are the striking features of the microscopical picture in the glands and intestine.

There seems no sufficient reason to correlate the intestinal,

PLATE XXXIII.
THE JOHNS HOPKINS HOSPITAL BULLETIN, SEPTEMBER, 1907.

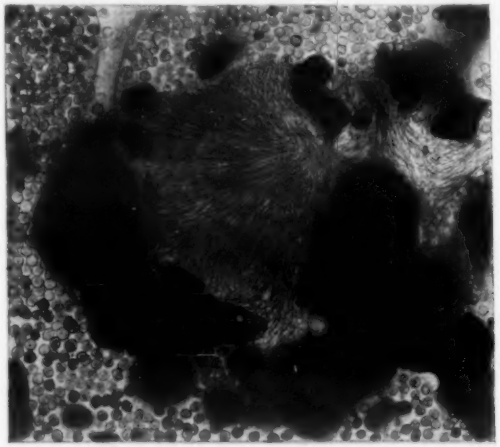


FIG. 1.—Frozen section of small mesenteric gland stained lightly with osmic acid. Rosette of fatty acid crystals and deposits of fat among lymphocytes.

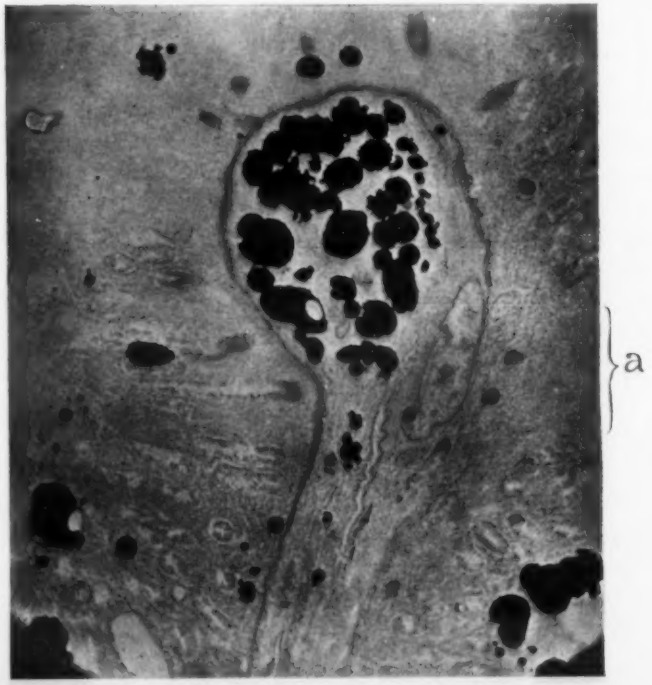


FIG. 2.—Marchi preparation. Cross section of one of the circular valves of the jejunum. Large central deposit of fat in the submucosa and on either side deposits in the mucosa. Soli-

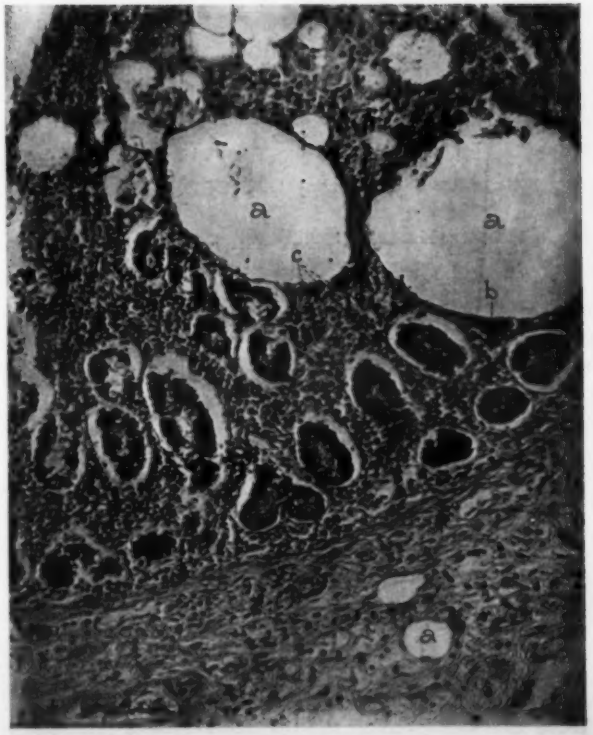


FIG. 3.—Fat vacuoles (*a*) in mucosa and submucosa. Giant

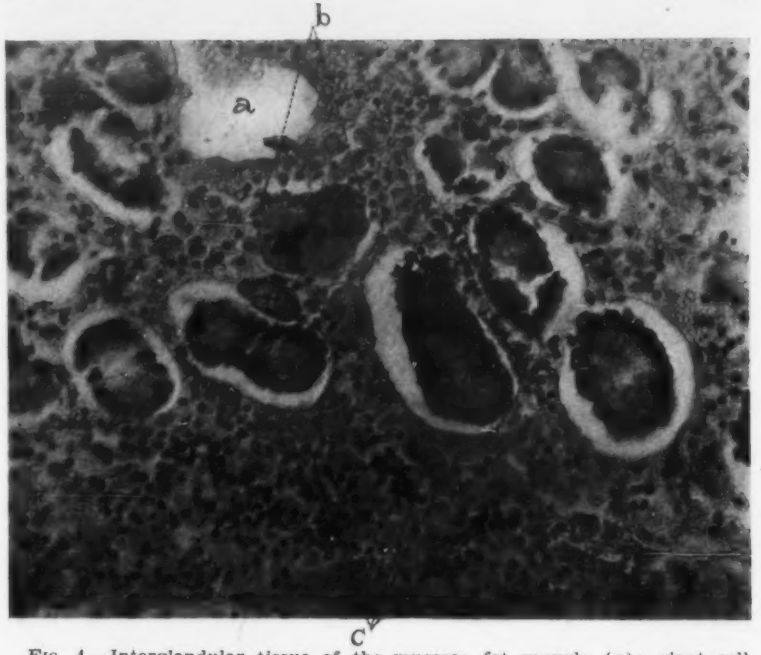


FIG. 4.—Interglandular tissue of the mucosa: fat vacuole (*a*); giant cell (*b*), and "foamy" cells (*c*). The muscularis mucosæ just appears at the base.

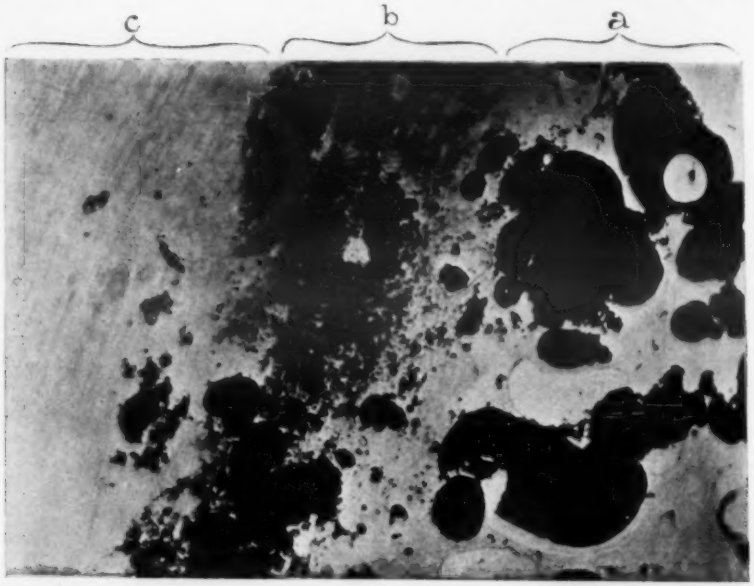


FIG. 5.—Marchi preparation. Cortex of large mesenteric gland. Large fat droplets (*a*); fine thickly placed fat droplets (*b*), and thick gland capsule free from fat (*c*).

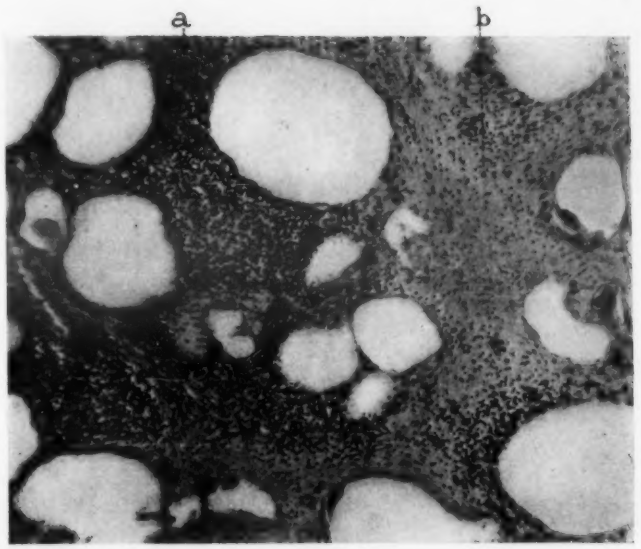


FIG. 6.—Large gland full of dense scar tissue (*b*); fat vacuoles lined with endothelium or giant cells. Normal lymphatic cells (*a*).

droplets (*a*), fine thickly placed fat droplets (*b*), and thick gland capsule free from fat (*c*).

lined with endothelium of giant cells. Normal lymphatic cells (*a*).

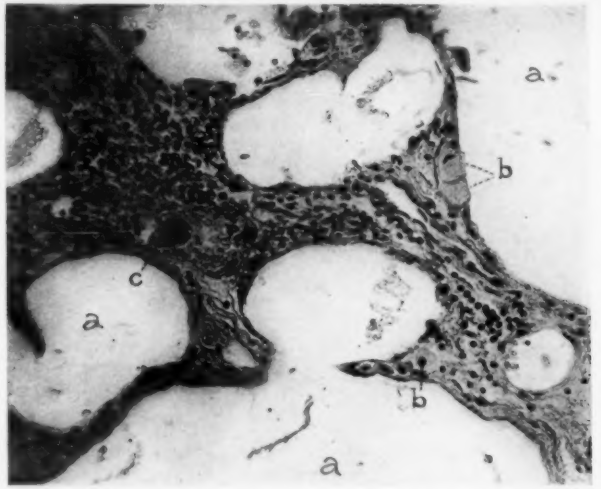


FIG. 7.—Large gland with thickly packed fat vacuoles (*a*); "foamy" cells at edge of fat deposit and in stroma (*b*); giant cell (*c*).

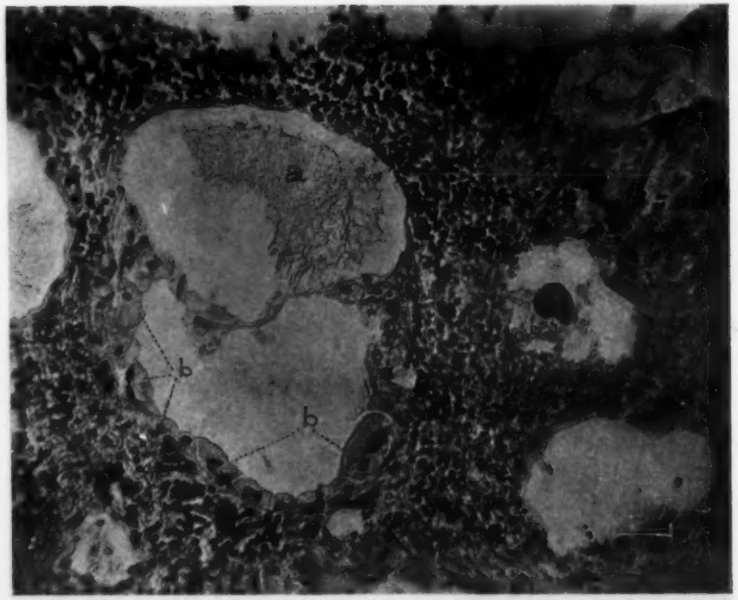


FIG. 8.—Small gland with more recent changes; red blood cells scattered through the tissues. Vacuole (*a*) contains a filmy granular coagulum. Rim of "foamy" poly- and mononuclear cells (*b*) at edge of fat deposit.

FIG. 9.—Section of gland stained by Levaditi method. Vacuole (*a*) containing rod-shaped organism (?).

arthritic, and serous lesions but it is possible that the organizing inflammatory reaction affecting the pleura, peritoneum, and aortic valve may be closely related to the peculiar arthritis and purpura which we were unable to examine at autopsy.

In searching for a name to designate this condition great difficulties were encountered. It would seem that no suitable name can be applied to it until the etiological factor is determined. The term *Intestinal Lipodystrophy* is suggested as this seems to offer less objections and to have more points in its favor than any one word or combination of words which have been considered.

In conclusion I wish to express by most sincere thanks to Dr. Thayer for his careful clinical analysis of the case which was under his care in the private wards, to Dr. Loevenhart for valuable assistance in the chemical study of the tissues, to Dr. Voegtlin for analyses of the stools and urine, to Dr. Ford and Mr. Harrison for the bacteriological examinations, to Dr. Welch and Dr. MacCallum for their interest and valuable suggestions, to Mr. Brödel and Mr. Ridges for assistance in preparing the illustrations.

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PANCREATITIS AND FOCAL NECROSES.

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In the following communication an attempt is made to show that the pancreas often presents minute focal necroses which at times may be related to fat necrosis and acute hæmorrhagic pancreatitis, as well as to some types of chronic diffuse pancreatitis. In the last 300 autopsies at the Johns Hopkins Hospital a careful study has been made of the pancreatic glands in 230 cases. The bile and pancreatic ducts were examined carefully. In many cases tissue was studied microscopically from the head, body and tail of the organ. When a single piece of tissue was examined it was usually removed from the tail. These cases may be grouped and classified as follows:

FOCAL NECROSES—41 CASES.

This group does not include the cases in the next three groups although many of them do show focal necroses. At times only a few very small necroses were found after long search, again many were found in a single lobule. Lobar pneumonia seemed to be the most active etiological factor, 11 cases; septicæmia, 6 cases; acute peritonitis, 6 cases; typhoid, 4 cases; bronchopneumonia (organizing), 3 cases; organizing endocarditis, 3 cases. The remaining cases were scattered (bronchiectasis, meningitis, collitis, hepatic cirrhosis).

The term "focal necrosis" is used to designate a type of focal degeneration affecting the pancreatic acini. The lesion usually appears as a granular change in the acinar epithelium with solution of the nuclei and rapid disintegration of the protoplasm. This change usually causes some increase in size of the affected acinus, and there is a very rapid invasion of polymorphonuclear leucocytes. In fact this change is recognized by the infiltration of leucocytes which may take place before the nuclei have vanished, although staining faintly (Fig. 1.). The basement membrane is quite resistant and as a rule remains intact even after all the acinar cells have undergone a granular degeneration and the membrane may only surround a granular detritus invaded by numbers of polymorphonuclear leucocytes. This change often affects acini which are dilated by pink colloid like casts and the colloid material may persist and be invaded by leucocytes after the acinar epithelium has been destroyed. These necroses as a rule are quite diffusely scattered through the parenchyma of the pancreas and quite small, commonly affecting but a single acinus or a part of one acinus. One may see a small segment of an acinus which shows a granular degeneration of its epithelium with invasion of 2 to 10 polymorphonuclear leucocytes in this tissue and in the lumen of the acinus. Frequently the necrosis will partially destroy the epithelium of 2 to 4 acini and there will be an invasion of leucocytes into their lumina and in the œdematous stroma between them. It is remarkable what a powerful attraction the degenerated acinar epithelium seems to have for the polymorphonuclear leucocyte. These small foci are soon invaded by mononuclear wandering cells (polyblasts) and fibroblasts, but usually a few polymorphonuclear leucocytes can be seen. 3 cases of organizing bronchopneumonia showed the changes just described, which appeared to be of about the same age as the pulmonary lesion but fresh foci were present as well. These small foci of degeneration which may contain many polymorphonuclear leucocytes do *not* as a rule contain bacteria. In a few of the cases of septicæmia where the necrosis involved several acini, clumps of bacteria could be demonstrated, but in not a single case of pneumonia with focal necroses could the organisms be demonstrated as having any regular relation to the degenerated tissue.

There is no regular association of pancreatic and liver necroses. In this series liver necroses were quite common in association with acute peritonitis. 23 cases of acute or organizing peritonitis showed liver necroses in 10, and pancreatic necroses in 6. 17 cases of lobar pneumonia: 8 showed no pancreatic necroses and 2 of these showed liver necroses; 9

showed pancreatic necroses and 2 of these showed liver necroses. Two of the cases showing thickly sown necroses in the pancreatic tissue, some of them involving 2 to 15 acini showed no liver necroses. 6 cases of septicæmia showed no pancreatic necroses. The term septicæmia as used here indicates cases in which antemortem cultures showed the presence of some organism in the blood or in which fresh and abundant cardiac vegetations were present. Liver necroses were found in 13 cases which showed no pancreatic necroses (pneumonia, typhoid, septicæmia, etc.).

Acute Diffuse Pancreatitis—6 Cases.

This group does not include cases which show any fat necroses, but only those cases presenting a diffuse inflammation of the parenchyma with numerous focal necroses in the acini and a diffuse infiltration of the damaged acini and œdematous stroma with many polymorphonuclear leucocytes (Fig. 2.). The older cases show invasion by polyblasts and fibroblasts, and a beginning organization. With a little experience these cases can be recognized at the autopsy if there is no advanced postmortem change. The organ is very pale and firm, sometimes almost of stony hardness. The ducts are clear and their walls thin. The lobules are large but clean cut and the parenchyma has a uniform semi-translucent watery gray color. It seems worth while to give a brief summary of these cases.

J. T. Colored male, 22 years. (Autopsy, 2700.)

Anatomical diagnosis.—Pseudo-lobar organizing pneumonia of both lungs; acute fibrinous pleuritis; acute bronchitis and lymphadenitis; focal necroses of liver; subacute pancreatitis; cloudy swelling of viscera.

Pancreas is large and extremely firm. The lobules are large and cleanly marked out. The parenchyma is semi-translucent, gray in color. The islands are visible as minute opaque pinpoint dots. Ducts quite normal. Bile ducts are clear throughout.

Microscopical study.—Sections from the head, body, and tail all show the same picture. There is a moderate amount of chronic diffuse increase in the stroma which is everywhere very œdematous and shows many wandering leucocytes and polyblasts (Fig. 2). In places there are young fibroblasts in the stroma. The acini show a focal granular degeneration with pale or non-staining nuclei, invasion by polymorphonuclear leucocytes as described in the scattered "focal necroses." Mitoses are present in some of the partially damaged acini. Many of the acini show dilatation of their lumina by deep pink staining colloid casts of various sizes. The interlobular stroma is not involved by the change which affected uniformly the delicate interacinar stroma. The ducts show no abnormalities. In places there is evidence of attempted repair by a loose granulation tissue of fibroblasts and polyblasts replacing 2 to 10 acini. Careful search for bacteria in sections revealed no organisms. Cultures from the lungs showed Micrococcus albus and aureus. 3 other cases showed an exactly similar picture: (1) Typhoid fever and peritonitis; (2) rapid pulmonary tuberculosis and bronchiectasis; (3) organizing bronchopneumonia and acute myositis. They all showed some grade of chronic cirrhosis as did the first case, liver necroses and a pancreas as described. 2 cases showed definite hyaline necroses of single acini or small clumps of acini, as well as the usual type of cell degeneration and solution. Ducts normal. No bacteria could be demonstrated in sections. 2 other cases showed in general the same picture, but bacteria were present in the sections. (1) Carcinoma of hepatic ducts involving the head of pancreas; jaundice; liver necroses. The pancreatic ducts were somewhat thickened, but not much dilated and not infected. There was a moderate degree of diffuse cirrhosis. (2) Acute leukæmia; acute nephritis, enteritis, and endocarditis. Ducts normal. There was no chronic cirrhosis of the pancreas, but merely the diffuse inflammation and scattered necroses. Bacteria could be demonstrated in some sections, but not in large numbers. The islands were normal in all this group of cases.

In all of these 6 cases we are dealing with a severe grade of toxemia as evidenced by the finding of liver necroses in 5, and pancreatic necroses in all. It seems probable that this very diffuse cellular reaction, in which the polymorphonuclear leucocytes predominate, follows some damage to the acinar epithelium. The following case makes a striking contrast to the preceding cases: (Autopsy, 2768) Chronic nephritis; acute general peritonitis. The pancreas shows an invasion of its interlobar stroma by a direct extension from the peritoneal inflammation. The interacinar stroma is only invaded slightly at the edges of the lobules and there are no necroses in the acini. Bacteria can be demonstrated in the œdematous interlobar stroma which is full of leucocytes.

These cases were all under careful observation in the wards of the Johns Hopkins Hospital, and gave no symptoms of pancreatic disease; and we may suppose this to be a reaction against some damage to the parenchyma by bacteria or their toxins, closely allied to the changes seen in some forms of acute nephritis. If the patients recovered such changes would surely go on to a chronic cirrhosis of the organ.

Fat Necroses—5 Cases.

These cases all show fat necroses in the pancreatic or peripancreatic tissues with no evident hæmorrhage. A brief summary follows:

(1) A. S. White female, 42 years. (Autopsy, 2710.)

Anatomical diagnosis.—Chronic pelvic peritonitis; stricture of rectum; operation and resection of rectum; fecal and urinary fistulæ; acute cystitis; double hydronephrosis; thrombosis of iliac and sacral veins.

Pancreas is very firm and rather small. Some areas are seen where there has been atrophy of parenchyma and replacement by greenish or gray semi-translucent tissue. In places the lobules are clean cut and easily separated from each other. No fat necroses seen in gross.

Microscopical sections from head, body, and tail show exactly the same picture as described in Autopsy 2700 (acute diffuse pancreatitis), but in addition the section from the tail shows three small typical fat necroses. These necroses are at the edge of lobules and not larger than 5 to 15 acini; they are surrounded by a halo of leucocytes and contain some bacteria as seen in sections. The tissue everywhere shows a diffuse pancreatitis with scattered focal degenerations or necroses. There is a slight grade of chronic diffuse cirrhosis. Ducts and islands are quite normal. Cultures from the viscera were sterile.

(2) S. White female, 23 years. (Autopsy, 2859.)

Anatomical diagnosis.—Chronic mitral endocarditis with stenosis; cardiac dilatation and hypertrophy; chronic passive congestion of viscera; cardiac thrombi; infarcts of lungs and kidneys; chronic diffuse pancreatitis with fat necroses; purpura.

Pancreas is enlarged and feels very firm and elastic. Cut section shows a pale grayish parenchyma on which the islands are quite conspicuous as minute opaque dots. The lobules are glued

together and vary greatly in size and shape. The head of the pancreas shows a most interesting condition. Scattered through this portion of the organ are numerous areas of opaque yellow color, not exceeding 1 mm. in diameter, oftentimes surrounded by a thin zone of hæmorrhage. Many of them are of typical chalky appearance. This change seems to be limited to the area supplied by Santorini's duct. The papilla of this duct appears to be normal. Its lumen is not dilated and it contains the usual slimy pale material. There are no hæmorrhages anywhere in the mucosa of this duct. The main duct opens into the papilla and is normal throughout in size and distribution. The vessels in this area appear normal. The lymph glands close to this area and along the body of the pancreas are of a deep purple color, but uniform on section. No necroses are seen.

Microscopical sections from various parts of the pancreas show the fat necroses to be localized in the head of the organ. They are situated at the edges of the lobules, of small size and outlined by leucocytes as a rule. Some of them show halos of fibroblasts and large mononuclear wandering cells (polyblasts). There is a very little blood pigment or fresh blood cells in some of these areas. The parenchyma everywhere shows a moderate grade of diffuse cirrhosis and extreme congestion of all its capillaries. The ducts and islands are normal. Numerous small focal necroses are present throughout all the sections and some of them show beginning organization. There is no acute diffuse inflammation. The distribution of these fat necroses suggests some agency of the duct of Santorini which may have been obstructed or infected, although there was no evidence of such changes.

(3) White female, 75 years. (B. V., 1907; autopsy, 82.)

Anatomical diagnosis.—Carcinoma of common duct; extreme icterus; extreme dilatation of hepatic ducts; liver necroses; chronic diffuse pancreatitis with fat necrosis; emaciation.

Pancreas very large, firm and pale. Ducts slightly dilated but smooth and patent. There is no obstruction at the papilla. There is glueing together of the lobules. One small area (2 mm. in diameter) is found in the tail which is of an opaque yellowish color and rather chalky appearance, suggesting a fat necrosis. No other necroses are found after careful search.

Microscopical sections from various parts of the pancreas show an extreme grade of chronic diffuse cirrhosis. One fat necrosis of the usual type is seen outlined by polymorphonuclear leucocytes. All sections show scattered focal necroses involving ½ to 5 acini and some show invasion by fibroblasts. The ducts are thick, but lined by normal epithelium. No hæmorrhages are present.

(4) W. A. B. White male, 56 years. (Autopsy, 925.)

Anatomical diagnosis.—Biliary cirrhosis of liver; icterus; ascites; chronic nephritis; bronchopneumonia; chronic pancreatitis with fat necroses.

Pancreas is large, gray, and firm. Just beneath the capsule are several whitish areas, the largest not over 5 x 1 x 1 mm. Numerous similar foci are found in the parenchyma on section, and they contain putty-like material. Bile ducts are quite patent.

Microscopical section shows a moderate grade of diffuse chronic cirrhosis. The ducts and islands are normal. Numerous fat necroses are seen at the edges of lobules, but no hæmorrhages. Focal necroses, some of which are organizing, are quite numerous in all the lobules. They are of small size, as a rule.

(5) A. F. White female, 72 years. (Autopsy, 2545.)

Anatomical diagnosis.—Carcinoma of bile papilla; icterus; dilatation of bile ducts; cholelithiasis; dilatation of pancreatic duct; pancreatic fat necroses; liver necroses.

Pancreas.—The head is very hard. A probe passed into the mass in the duodenum goes into the pancreatic duct which is enlarged, measuring 23 mm. in circumference. On opening this orifice it is found to be surrounded by a collar of opaque grayish white tissue exactly similar to that round the orifice of the common bile duct. This new growth seems to extend irregularly into the underlying pancreatic tissue. The distal portion of the pancreatic duct is enormously dilated and very tortuous. Its lining presents a peculiar beaded appearance. The pancreas on section is smooth and hard. It contains several cyst-like structures probably the result of retention. There is considerable infiltration with adipose tissue which here and there shows small chalky fat necroses.

Microscopical section shows a moderate grade of diffuse cirrhosis and fat infiltration. There are numerous typical fat necroses involving the edges of the lobules. No hæmorrhages are seen. Focal necroses are quite numerous and many polymorphonuclear leucocytes are seen in these areas and in the œdematous stroma. The islands are normal. The duct epithelium shows a metaplasia to a stratified type, and there is some inflammation of these structures whose walls are thick and much dilated. It is possible that there has been an infection of the obstructed ducts, but there could have been no retrojection of bile through the constricted and cancerous duct and papilla.

These 5 cases all show more or less chronic diffuse pancreatitis and focal necroses, suggesting that these are predisposing factors in the development of fat necroses. Icterus is present in 3 cases. The changes in all are rather slight, only one small fat necrosis in the entire pancreas of one case—and can be easily overlooked. Perhaps a more rapid extension of the process would lead to hæmorrhages, and the familiar lesion of hæmorrhagic pancreatitis.

ACUTE HÆMORRHAGIC PANCREATITIS—7 CASES.

Very brief abstracts of these cases will be given.

(1) Black male, 40 years. (Autopsy, 2820.)

Anatomical diagnosis.—Chronic diffuse nephritis; cardiac hypertrophy; general arterio-sclerosis; bronchopneumonia.

Pancreas is quite pale, but the ducts and parenchyma appear normal. Gall ducts and bladder normal.

Microscopical sections from head, body, and tail show a slight amount of cirrhosis in the head and body, but a more advanced chronic fibrosis in the tail. Duct and islands are quite normal. Section from the tail shows a few minute typical fat necroses and slight extravasion of well preserved red blood cells into the adjacent stroma. *This focus escaped the gross examination. Focal necroses are present in this section, but absent in those from the head and body. Surely this case is closely related to the previous group of fat necroses and probably there is no sharp dividing line. This case again emphasizes the fact that chronic cirrhosis of the pancreas seems to predispose to the focal necroses as well as the fat necroses.*

(2) White female, 13 years. (Autopsy, 2855.)

Anatomical diagnosis.—Bronchopneumonia; acute hæmorrhagic pancreatitis with fat necroses; focal necroses of liver; cystic remains of thyroid; cretinism.

Pancreas presents an unusual appearance. About its distal portion are a few small areas of fat necrosis, one measuring 4. mm. in diameter. The tissue immediately anterior to the body is quite œdematous and of a bloody appearance. The organ measures about 11 cm. in length, and is of normal shape and consistency. The external surface presents numerous lobules, of a whitish yellow color, surrounded by a reddish network. Numerous minute hæmorrhages are present. Other lobules are of a deep brown and purple color, some quite translucent. On cross section the same lobulation is visible as described, but the organ is made up almost entirely of whitish irregular lobules. A few pin-head areas of focal necroses are present. The duct contains a slight amount of gelatinous mate-

rial, but is everywhere clear on dissection with the scissors. It is found to empty beside the bile duct at the ampulla, but is not bile stained. The gall bladder and ducts are normal.

Microscopical sections from various parts of the organ show normal stroma and ducts. All sections show a very diffuse and recent type of hæmorrhagic inflammation and necrosis of the parenchyma and fat cells. The polymorphonuclear leucocytes and red cells are well preserved. Lobules which are not involved by the hæmorrhages show scattered focal necroses of the usual type affecting one or several acini.

(3) White female, 52 years. (Autopsy, 2869.)

Anatomical diagnosis.—Cholelithiasis; carcinoma of hepatic ducts; icterus; dilatation of pancreatic duct; chronic pancreatitis; pancreatic fat necroses; thrombosis of iliac vein.

Pancreas is somewhat enlarged and quite firm. There are numerous hæmorrhages which show through the overlying peritoneum, but which are very small and superficial. Opaque areas of necroses also show through from the pancreatic tissue. On section the pancreas is found to be separated into lobules by a grayish œdematous fibrous tissue. In places the lobules stand quite far apart. There are numerous necrotic patches throughout the gland, the larger being 1 cm. or more in diameter. In these areas the tissue is reduced to a green opaque pulp, which is apparently outlined by a beginning capsule. The necroses are more abundant toward the tail where every section shows a number of them. The pancreas near the head shows fewer of them, and the head itself is practically quite free. The duct is greatly dilated. In the tail it is about 3 mm. in diameter, but toward the junction of the middle and the head, it becomes dilated to 6 to 8 mm. in diameter, contracting again sharply at a sudden curve to a diameter of about 4 mm., which it maintains to its opening at the papilla, which, as stated, lies side by side with that of the bile duct. The ampulla is not so prolonged as to suggest a possible retrojection of bile. There are many branches from this duct, but no special duct of Santorini was found. There is no obvious cause for the dilatation of the duct. Its mucosa looks slightly scarred. It contains a glary opalescent colorless fluid. The very sclerotic splenic artery courses through it.

Microscopical sections show a moderate degree of diffuse cirrhosis. The ducts are dilated and thickened, but show no acute process. The islands appear normal. There are numerous recent and organizing fat necroses in the lobules and at their edges. There is the usual picture of an acute hæmorrhagic inflammation in many areas, but this change is absent in many lobules. Here we may find scattered focal necroses in the acini; some of them are of the hyaline type and quite small as a rule.

(4) Black female, 28 years. (Autopsy, 2775.)

Anatomical diagnosis.—Retroperitoneal and retropancreatic hæmorrhage; disseminated fat necroses; large retroperitoneal hæmatoma; anæmia. Pancreas is of normal size and consistency. Its tail is included in the necrotic hæmorrhagic extravasation. The duct is normal. The parenchyma shows scattered fat necroses. Gall bladder and ducts normal.

Microscopical sections show an advanced type of very diffuse cirrhosis. Large areas of necrosis of fat and parenchyma are seen which are outlined by large wandering cells and fibroblasts—they are evidently of some age. No recent focal necroses are found, but scattered areas in which there has been a disappearance of the acini with replacement by fibroblasts and polyblasts. We may look upon these as areas of focal degeneration or necrosis which are of the same age as the fat necroses and are undergoing organization.

(5) White male, 69 years. (Autopsy, 2812.)

Anatomical diagnosis.—Myelogenous leukæmia; submucous and subserous ecchymoses; necroses in liver; cholelithiasis; acute hæmorrhagic pancreatitis.

Pancreas is considerably enlarged, and greatly softened. It presents a mottled grayish purple appearance due to the fact that there are small recent hæmorrhages between many of the lobules which are swollen, soft and of a grayish pink color. A few minute fat necroses of pin-point size and chalky white color are seen in the gland substance. No fat necroses are seen in the surrounding tissue. The lobulation is hard to make out because of the softening and hæmorrhages, but it seems somewhat irregular. The pancreatic duct is clear and opens freely into a well-formed diverticulum of Vater. A stone could have blocked this opening and caused a retrojection of bile into the pancreatic duct, but there was no evidence of this.

Microscopical sections show considerable post mortem changes which have obscured the details. There is an advanced type of diffuse cirrhosis plus the usual hæmorrhagic change.

(6) Black female, 40 years. (Autopsy, 2879.)

Anatomical diagnosis.—Myocarditis; chronic passive congestion of viscera; pelvic and cardiac thrombi; pulmonary infarcts; liver necroses; hæmorrhages in pancreas.

Pancreas is of about normal size, but very soft and flabby. On section the parenchyma is almost diffluent, but shows here and there scattered areas of purplish hæmorrhage, 2 to 3 mm. in diameter, which merge gradually into the parenchyma. These are most numerous in the body, but present in the head and tail of the organ.

Microscopical sections show a definite hæmorrhagic inflammation of the pancreas with invasion of leucocytes at the edges of these areas. There is a moderate grade of diffuse cirrhosis, but none of the finer changes can be made out because of autodigestion.

(7) White female, 65 years. (Autopsy, 2860.)

Anatomical diagnosis.—Carcinoma of gall bladder (cholelithiasis); invasion of liver, duodenum and common duct; extreme icterus; hæmorrhagic pancreatitis; subserous, submucous and subcutaneous hæmorrhages; bronchopneumonia; liver necroses.

Pancreas is enlarged throughout, but this enlargement is most marked in the caudal portion. In the terminal 5 cm. of the pancreas the organ is found to be greatly enlarged, firm and elastic. It is of triangular cross section, measuring about 4 cm. on a side. The fat in the immediate neighborhood shows a great deal of dark purplish hæmorrhage and some scattered foci of orange yellow opaque chalky appearance. The pancreas itself on section shows numerous opaque chalky dots of varying size and a few areas of blackish green necrosis, measuring 4 to 5 mm. in diameter. Only a few small hæmorrhages are seen in the parenchyma of the pancreas. The hæmorrhages being most conspicuous in the fat in the immediate neighborhood of the pancreas. In one small area about 3 cm. from the tail of the pancreas, the parenchyma and fat near by show a most remarkable change. The tissue is of a mottled appearance, areas of deep purple alternate with yellow opaque areas, or areas of green color, which are usually very dry and chalky. These appear to be older than the areas of yellow necrosis. The body of the pancreas shows hæmorrhages in places, which are usually confined to the subserous peritoneal tissue, but orange yellow necroses are found throughout the parenchyma, varying from pin-head size up to 2 mm. in diameter. As one approaches the head of the gland the change becomes less striking and only occasional foci of orange yellow opacity are found. A few ecchymoses, but no large hæmorrhages are seen in the head of the pancreas. The duct is very carefully dissected out and found to be perhaps slightly dilated. Its intima shows no bile staining. Its wall does not appear to be thickened. The duct opens on the lateral aspect of the bile papilla described above, but their orifices are quite distinct from one another. The pancreatic duct in this location is not thickened and rigid as is the common bile duct. There seems to be some diffuse increase in connective

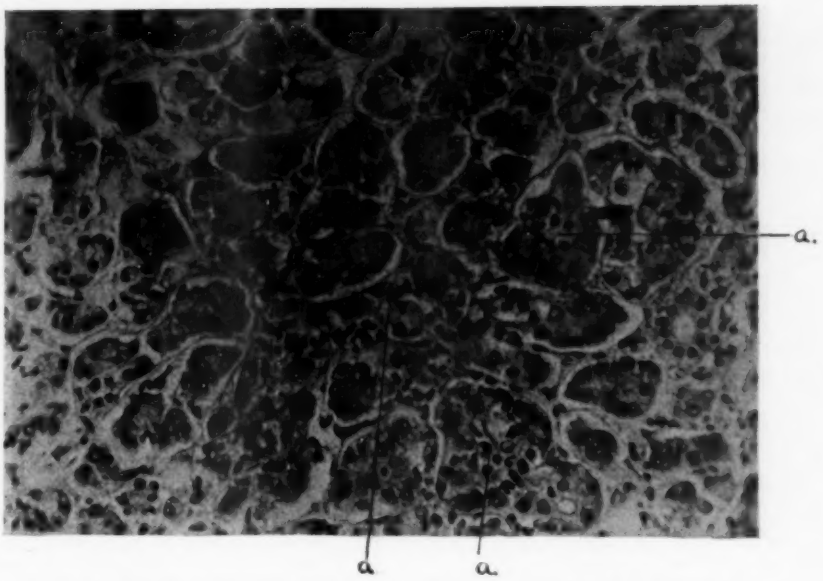

FIG. 1.—Pancreas in case of lobar pneumonia; (*a*) "focal necroses" in acini; cell degeneration and leucocytic infiltration with preservation of the architecture.

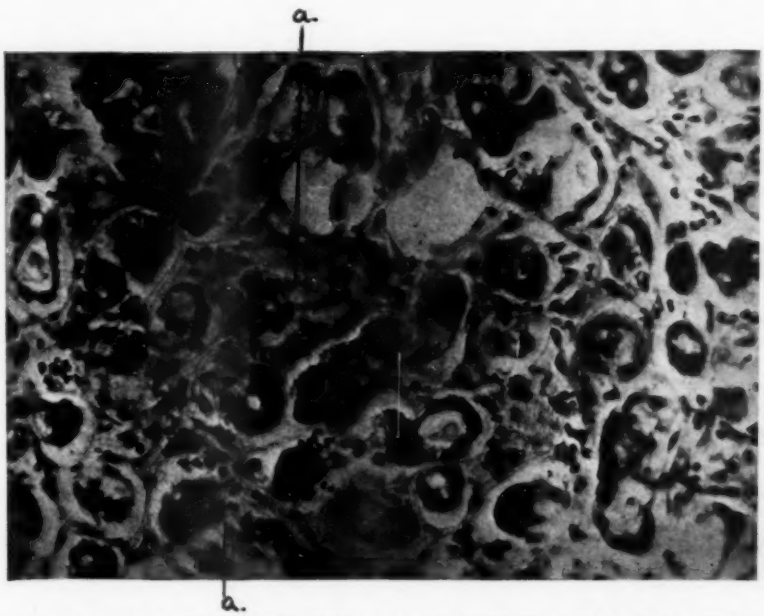

FIG. 2.—Acute diffuse pancreatitis; (*a*) focal necroses in acini. The stroma shows a diffuse infiltration with leucocytes.

tissue between the lobules of the gland, which are definitely glued together.

Microscopical sections show a slight diffuse cirrhosis of the organ. The usual type of fat necrosis and hæmorrhagic infiltration is found, but no focal necroses can be made out in the acini. A few of the smaller ducts show an exudate of leucocytes and a fine granular coagulum in their lumina. They are dilated, and it is possible that there has been an ascending infection from the duodenum, but there could have been no retrojection of bile except by the agency of duodenal contraction.

These 7 cases show several points of interest. The focus of hæmorrhagic necrosis and inflammation may be very small and located in the tail of the organ. Such cases are closely related to those in the previous group of "Fat Necroses." 4 cases show focal necroses in the tissue which is not involved by the hæmorrhage or fat necrosis. 2 cases present so much postmortem change that minute details are obscured. One case shows no focal necroses, but many of the pancreatic ducts give evidence of an acute inflammation. 6 cases show more or less diffuse cirrhosis of the pancreas. 4 cases show liver necroses and 3 icterus. These cases emphasize the relation of chronic pancreatitis and focal necroses to the extensive fat necroses and hæmorrhagic pancreatitis. It is probable that icterus is a predisposing factor. To gain additional evidence on this point a series of 15 cases of icterus was studied. The majority of these cases showed gall stones, or cancer of the ducts. 4 cases presented diffuse cirrhosis and focal necroses; of these cases 2 showed the common type of acute hæmorrhagic pancreatitis. This would indicate the combination of icterus, focal necroses and chronic diffuse pancreatitis as a powerful factor in determining the onset of the hæmorrhagic necrosis.

Chronic Pancreatitis.

An attempt was made to classify the chronic changes in the pancreases in 222 cases. Four classes of cirrhosis were arbitrarily fixed and the pancreatic glands grouped according to the degree of cirrhosis shown by microscopical study. 105 cases showed a perfectly normal stroma.

Class 1. 20 cases showed a very slight grade of diffuse increase in stroma or a few patches of cirrhosis here and there. It is possible that such cases come within the limits of normal gland tissue.

Class 2. 41 cases presented a slight but definite grade of cirrhosis. A single case showed an annular type of change with involvement of the interlobular stroma, but the rest of the cases showed a diffuse interacinar change. A few of these cases showed many dilated acini which often were filled with pink colloid-like casts.

Class 3. 40 cases presented a moderate grade of diffuse cirrhosis involving the interacinar stroma. This change usually caused considerable distortion of the acini with dilatation of their lumina, and the colloid casts were often present. When the acini became dilated their epithelial cells often showed an acid staining finely granular protoplasm and nuclei which were slightly shrunken or normal in appearance. Such cells may make up half the circumference of a dilated acinus while the remaining cells may present the usual granular lilac staining protoplasm and normal nuclei. Because these "acid" cells were often seen in dilated acini filled with a colloid material it was thought that they represented quiescent cells or possibly slightly degenerated ones. With these cells we may compare a different type of pancreatic cell which shows a granular or uniform acid staining protoplasm, and rather dense or normal nuclei. Such cells were seen in about 20 per cent of the tissue examined and they may occur in single acini or large clumps of acini (20-60). These acini did not as a rule show any dilatation and the cells were plump, of normal contour and size. At times an acinus may be found showing these "acid" cells, and the usual pancreatic cell side by side. The significance of these "acid" cells is not clear, but they may be resting cells.

Class 4. 12 cases showed an advanced type of diffuse cirrhosis. 1 case showed an annular type of interlobular cirrhosis but there was a diffuse interacinar change as well. In the majority of these cases the fibrous tissue was dense and poor in nuclei, but in 2 cases it was quite rich in cells and evidently of a more recent formation. The distortion of the acini was great and many peculiar forms were seen. In some cases it seems sure that the acini give off buds which grow into the stroma, and in a few cases mitoses were seen. The small ducts, too, grow into this new formed connective tissue and send sprouts out in many directions, some of which take on the appearance of newly-formed small acini. Many of these cases showed fat infiltration between the shrunken lobules as well as inside the lobules, and cirrhosis of the pancreas seems to predispose to fat infiltration, not depending on the general nutrition. Some cases showed no fat infiltration, even with advanced cirrhosis. Where fat infiltration was found in a comparatively normal gland the general fat deposits were considerable.

Class 5. 3 cases presented an extreme degree of cirrhosis. One was particularly interesting. This case showed a pancreatic calculus situated in the body of the organ. The distal ducts were greatly dilated and the tail of the pancreas was a dense mass of fibrous tissue enclosing a few remnants of acini, ducts, and well preserved islands. The ducts showed great distortion and many buds growing into the stroma. It seems probable that this is a weak effort at regeneration resembling the active efforts of the bile ducts in hepatic cirrhosis. The fat tissue about the tail showed many scars of dense fibrous tissue, and one of these contained much yellow granular blood pigment, suggesting that at some previous time there had been a local area of fat necrosis and hæmorrhage which had undergone complete organization.

The islands of Langerhans were examined with considerable care in all these cases. Very rarely were they the seat of any sclerosis, even when the parenchyma was extremely sclerotic. 2 cases showed hyaline degeneration. Autopsy 2799 was a case of tetanus which showed a slight grade of diffuse cirrhosis of the pancreas. A few of the islands showed a hyaline sclerosis and obliteration, but the majority were normal. Autopsy 2895 was a case of chronic nephritis which showed an advanced diffuse cirrhosis of the pancreas. Many

of the islands in the tail showed hyaline degeneration and sclerosis. Sections from the body showed the same change in the islands, but a smaller percentage were involved. Neither case showed diabetes. 2 cases of diabetes were included in this series. Autopsy 2782 was a case of hemochromatosis with extreme cirrhosis of the liver and pancreas. The islands were quite well preserved, in striking contrast to the acini which showed extreme degeneration, their cells being crowded with yellow pigment which was almost absent in the cells of the islands. Autopsy 2650 was a case of diabetes terminating fatally from a secondary infection. The pancreas showed a moderate grade of diffuse cirrhosis, but the islands were quite normal.

The islands in the following case (Autopsy, 2747) were sufficiently abnormal to deserve mention. The case was that of a strong healthy boy of 6 years who died from a septicæmia developing from a tonsillar abscess. The pancreas presented a normal stroma. The islands were more numerous than normal and of peculiar cylindrical shape, often coiled or twisted. They were made up of double rows of high cylindrical epithelium having pale protoplasm and rather small oval deep staining nuclei situated in the outer third of the protoplasm, near the basement membrane. The limiting membrane was sharply outlined and these cylindrical masses of cells often showed well marked lumina with single rows of cells on each side. In several instances one could trace out a direct connection between the small interlobular ducts and these islands with a gradual transition of epithelium. No islands of the usual type were seen.

4 cases of extreme chronic passive congestion presented some interesting changes in the islands. The capillaries in many islands were dilated to such an extent as to cause almost complete atrophy and disappearance of the cells. Two cases showed hæmorrhage into the capsules of the islands with destruction of the cells, but no rupture of the capsules which were thickened. This was an occasional finding and the majority of the islands were normal.

Conclusions.

1. "Focal necroses" are found in the pancreas in many acute intoxications: pneumonia, septicæmia, peritonitis, typhoid fever. (Fig. 1.)

2. The same necroses are present in acute diffuse pancreatitis (Fig. 2) and in many cases of fat necrosis and hæmorrhagic pancreatitis. It seems probable that these necroses are factors which predispose to pancreatic fat necrosis and hæmorrhage.

3. Chronic diffuse pancreatitis and icterus as well are important predisposing factors.

4. "Focal necroses" and acute diffuse pancreatitis may be the etiological factors in some cases of chronic diffuse pancreatitis.

5. A moderate degree of cirrhosis of the pancreas is a common finding at autopsies.

6. The islands of Langerhans are rarely involved by this cirrhosis.

NOTES ON NEW BOOKS.

Clinical Psychiatry. A Text-Book for Students and Physicians. Abstracted and adapted from the seventh German edition of Kraepelin's "Lehrbuch der Psychiatrie." By A. Ross Diefendorf. New edition, revised and augumented. (*New York: The Macmillan Company, 1907.*)

When Dr. Diefendorf issued his first edition of this book he undoubtedly did great service to the promulgation of the views of Emil Kraepelin and consequently, to the advancement of the clinical method of the study of psychiatry. Before this time (1902) there did not exist any work in English where Kraepelin's views might be studied except in a few isolated instances where a part of his work had been translated, as, for example, Dr. Brownrigg's translation of a part of the section upon dementia præcox. At the time of the first publication of this book the question was asked whether Dr. Diefendorf had been quite fair to Kraepelin in abridging his work and in interpolating matter of his own, but it must be borne in mind that the work of Kraepelin is a large two volume affair and a mere translation would not be as valuable to English readers as an adaptation. Further, the student would not purchase so large a work which would necessarily cost from eight to ten dollars and the time allowed the course of psychiatry in most American medical curricula would not permit of a proper study of such a work. It must be admitted, therefore, that Dr. Diefendorf accomplished the greatest good by his abridgment, and made a text-book which would attract both teacher and student. The objection that by this abridgment the clearness of Kraepelin's views has suffered is not substantiated by a study of the work.

In the present edition considerable new matter has been added from a later addition of Kraepelin and certain parts have been still further abridged as they have been found too full for class room use, for example, the laboratory method of psychological examination has been omitted while the method of general examination has been enlarged by the addition of a number of practical suggestions. There has also been added an abridgment of Kraepelin's chapter on the classification of Mental Diseases, and of the chapter on Psychopathic Personalities which did not appear in Kraepelin's earlier editions. From all standpoints this book is one of the best we have for the student of psychiatry.

In mechanical details the whole is first-class.

W. R. D.

Text-Book of Psychiatry. A Psychological Study of Insanity for Practitioners and Students. By Dr. E. Mendel. Authorized translation, edited and enlarged, by William C. Krauss, M. D. (*Philadelphia: F. A. Davis Company, 1907.*)

This work fulfills many of the demands of popularity in being concise, convenient in size, and reasonable in price, so that there is no reason why it should not meet with success, but while its brevity is of value to the person who wishes to use it as a review, or to enable him to pass an examination, to the student who is first introduced to psychiatry in these pages the brevity may prove a source of confusion unless his teacner is able to go over the book with him page by page and elaborate the knowledge he is acquiring by the examination of considerable clinical material. To the student who has been so fortunate as to acquire a clinical

experience with the insane, this book will be of great value in aiding him to arrange his facts in logical order.

The first 160 pages are devoted to General Psychiatry and are divided into: (a) General Symptomatology, with chapters on Disturbances of Sensation and Sense-perception, Disturbances of Thought, Disturbances of Reproduction (Memory), Disturbances of the Feelings (including Sensory Feelings and Feelings of Judgment), Disturbances in the Condition of the Mind (Emotions), Disturbances of Consciousness, Disturbances of Self-Consciousness, Disturbances of Action, Disturbances of Speech, Writing, and the Expression of the Countenance, Pathological Disturbances in the Condition of the Body, and Anomalies of the Internal Organs; (b) The Etiology of Mental Diseases; (c) Outbreak, Course, Duration, Results of Psychoses; (d) Pathological Anatomy of Mental Diseases; (e) Diagnosis of Mental Diseases; (f) Prognosis of Mental Diseases; (g) General Treatment. A number of the above are also divided into chapters.

The second part on Special Psychiatry occupies 117 pages and is divided into: I. Idiotism, II. Functional Psychoses, III. Psychoses Arising from Central Neuroses, IV. Psychoses of Intoxication, V. Organic Psychoses. As stated in the preface the objection may be made that the above classification "is not wholly free from objection," but will "enable the physician to make a diagnosis in the great majority of cases." This objection is pretty sure to be made by quite a number and especially by those who are accustomed to the classification of Kraepelin, which seems more logical and better defined than that of Mendel.

Quite a number of criticisms may be made of various statements, though in many cases these would be merely expressing a difference of opinion, but the therapeutics as a whole are bad and the free use of the bromides which is advocated, if followed, is bound to produce a number of terminal dements. The use of duboisin and morphia as hypnotics can only be condemned, and the general treatment by hydrotherapy, rest, isolation, occupation, etc., is too briefly touched on.

The work of Dr. Krauss has been well done, and especially in the added matter has he shown good judgment. The supplement containing a form for examination of patients suffering from mental disease is a valuable addition. It is a pity, however, that there are occasional inequalities in the translation which interfere with an easy understanding of the text, the most marked example occurring on page 273. W. R. D.

International Clinics. Vol. II, Series 17. (*Philadelphia and London: J. B. Lippincott Company, 1907.*)

This volume contains 25 articles, four on treatment, medicine, surgery, gynæcology and neurology; three on pathology; and two on pædiatrics; 17 are written by men in the United States, and the remainder by foreigners, among whom may be mentioned Dieulafoy and Letulle, of Paris; Clogg and Lockyer, of England. Cole, Rotch, Flexner, Dock, and Burr are some of the American contributors. Such names as these show how well maintained is the international character of this publication, and its merit. With the constant demands made on the leaders in medicine throughout the world to furnish papers for all sorts of meetings, books, and periodicals, the mark of success of these clinics is in its list of contributors. The first paper in this volume is a timely one on the Vaccine Treatment of Infectious Diseases, by Cole. So much attention has been given to this subject since Wright's original papers, that a careful résumé of the subject, such as Cole here offers, is valuable to all students of medicine. Rous in a similar manner has dealt with The Clinical Examination of the Cerebrospinal Fluid, and in association with this paper should be read Flexner's Experimental Cerebrospinal Meningitis. All the contributions are worth reading, but it is not possible to give the name of the author and title of each. As much praise cannot be given the illustrations, which are often superfluous, and but poor reproductions. One or two good plates are worth a dozen poor ones. R. N.

Nephritis. A Manual of the Disease Commonly Called Nephritis or Bright's Disease, and of Allied Disorders of the Kidneys. By SEELYE W. LITTLE, M. D. (*New York: The Grafton Press, MCMVII.*)

The object of this manual as the author states in his preface is to consider "nephritis as a clinical rather than a pathological phenomenon," and from this point of view Dr. Little has written a useful little book. All readers are not likely to agree that "the disease called nephritis is a step in this evolutionary process towards eliminating individuals with kidneys below a very high standard of efficiency" (p. 32) or that "it is probable that humans have for generations been developing a more and more highly efficient kidney" (p. 33). If this be true of the kidneys, it is equally true of all the other organs of the body, and there is as yet no proof of such evolutionary changes in man. These views of the author do not diminish the good in what he writes, but rather add interest to his work. The Grafton Medical Books are attractively published. They are of a pleasant size and type. R. N.

Notes on Blood Serum Therapy, preventive Inoculation and Toxin, and Serum Diagnosis. For Veterinary Practitioners and Students. By WALTER JEWETT, F. R. C. V. S., D. V. H. (*Chicago: W. T. Keener & Co., 1907.*)

This small book of 200 pages will be of undoubted value to those for whom it is intended. The known general principles of immunity are briefly described and a short statement in regard to the nature of the immunity and the methods for artificially conferring it in each of the best known infectious diseases of animals is given. The discussion is too brief, however, and the statements too dogmatic, considering the tentative nature of much of our knowledge along the lines treated, to make the book of much value to those interested in comparative pathology, or, in fact, to any except those desiring only the most simple and rudimentary knowledge on the subject. The directions, too, for the various diagnostic and other procedures are not given with sufficient detail to make the book of value as a working guide.

The writer is familiar, however, with the latest contributions, and the work of selecting the most important facts have been well done. This small treatise will probably be much used by veterinary students, and is valuable for those desiring to obtain very brief but reliable information concerning immunity in animal diseases.

Foods and their Adulterations. By HARVEY W. WILEY, M. D., Ph.D. (*Philadelphia: P. Blakiston's Son & Co., 1907.*)

Dr. Wiley is so well known to the medical profession as an authority upon the chemistry of foods and the results of his numerous investigations have been so largely appreciated, that this volume, which may be said to express the most positive of his convictions, will find a ready welcome. To those medical men especially interested in questions of public health, the book is thrice welcome, since we have hitherto had in this country no very authoritative expression of opinion upon a number of questions very closely bound up with the national well-being. The book is divided into ten parts, each of which takes up in detail a consideration of a group of allied food products, and it is so conveniently arranged as to afford the reader easy access to the portion dealing with any one particular food. Thus, Part I treats of Meat and Meat Products; Part II of Poultry, Eggs and Game Birds; Part III of Fish Food; Part IV of Milk and Milk Products and Oleomargarine, etc. In these various parts the author has given us an encyclopædic list of practically all the food products known, accurate tables of their chemical composition, data as to their nutritive

value, notices of the various adulterants employed in counterfeiting the genuine article, and finally much technical information as to the chemical substances ordinarily employed in their preservation. In addition to these ten parts, there is an Appendix of over a hundred pages, giving the enactments of the United States Government in regard to the composition of food, the meaning of various trade names and terms, the laws relating to packing and shipping foods, the amount of preservative and coloring matter which may be legally added to food products and a mass of other valuable information. The book is profusely illustrated and these illustrations, with the exception of the colored plates of the various cuts of beef, loaned by Armour & Company, of Chicago, which depart in color very far from the cuts of meat as actually seen in the markets, are fairly well done.

The most interesting and possibly the most valuable portion of the book is Part I, dealing with Meat and Meat Products. Here we find excellent tables giving the composition and the nutritive value of the flesh of different species of animals, of different cuts of the same animal, illustrations of the proper methods of preparing meat for the wholesale and retail market and especially extensive descriptions of the procedures in vogue in canning this product. The subject of preservation is taken up very fully and while we are inclined to agree with Dr. Wiley in the position he takes as to the harmful effects of preservatives upon the animal economy, it is to be regretted that he has not given us more technical information upon a number of points. Many of the original publications of the author upon this phase of the subject have been published in the Reports of the Department of Agriculture and do not find their way into the general literature. For this reason it is important that the reader should be able to obtain in Dr. Wiley's own book, the most convincing results of his many experiments. One would like, for instance, to know the actual amount of various preservatives, such as borax or sulphite of soda, which has been proved to be injurious to man, the amount of such preservatives which has actually been found in meat purchased in the open market, and the percentage of such chemicals which, in Dr. Wiley's opinion, can be added to meat with entire safety to the consumer. The public, unfortunately, is certain to eat meat containing preservatives. How far then will it suffer in so doing? In this section dealing with Meat and also in that treating of Milk, the question of tuberculosis has received inadequate treatment. Because this is undoubtedly the most important problem in the entire range of foods and a lack of agreement among authorities upon some of the minor details is not a good excuse for failure to present the results of countless investigations submitted by scientific men the world over. One looks in vain in Dr. Wiley's book for definite statements as to the amount of tuberculosis in different species of animals, its prevalence in various parts of the country, the harmfulness of the flesh of animals with advanced generalized tuberculosis, the appearance of such tuberculous meat, the harmlessness of meat from animals having localized tuberculosis, and the economic value to the nation of the use of such food under proper precaution by the poorer classes. Again, little is said as to the effect upon man of the consumption of milk from tuberculous cattle, or of the effect of feeding such milk to other species of animals in the propagation of the disease.

In general, however, the information given in the book is adequate and satisfactory, the subject matter is presented with admirable simplicity and the volume is a great credit to the author and may be cordially recommended to the public.

Manual of Clinical Chemistry. By A. E. Austin A. B., M. D., etc. (*Boston: D. C. Heath & Co., 1907.*)

In this small 12mo of 278 pages it is the aim of the author to combine the "practical part" of Medical Chemistry, Physiological Chemistry and the modern methods of analysis, leaving out all that is unnecessary or confusing to the student. The ambition is a laudable one, but we think rather difficult of attainment. In our opinion it is hardly possible to give a student without rather thorough basal training in general chemistry and physics, any material grasp of Clinical Chemistry. And without the knowledge of the reason for various changes and tests, he is likely to be a mere parrot in his work and become a confirmed rule-of thumb text-book diagnostician.

We hardly agree with the author that he has accomplished the task laid down in his preface, and although the book is readable and intelligible to one who is trained, it would hardly fit the student for discerning chemical diagnosis.

Physical Diagnosis. By Howard S. Anders, A. M., M. D., etc. (*New York: D. Appleton & Co., 1907.*)

In this work the author presents a compilation of Physical Diagnosis with no very extensive or valuable personal contributions either in method or interpretation. The reproductions of Butler's plates and the radiograms by Dr. Pfahler are very good, as is the letter press and general appearance of the work.

With many excellent works already available and kept up to date, there seems hardly any pressing need for this.

Hare's Therapeutics. A Text-Book of Practical Therapeutics, with Especial Reference to the Application of Remedial Measures to Disease and their Employment upon a Rational Basis. By Hobart Amory Hare, M. D., B. Sc., Professor of Therapeutics and Materia Medica in the Jefferson Medical College of Philadelphia, etc. New (12th) edition, enlarged and thoroughly revised to accord with the eighth decennial revision of the U. S. Pharmacopœia. In one octavo volume of 939 pages, with 114 engravings and four colored plates. (*Philadelphia and New York: Lea Brothers & Co., 1907.*)

Perhaps no other medical text-book which has appeared in the last twenty years has had such a deserved success as Hare's Therapeutics, and it is a pleasure to congratulate both the author and the publisher on this work. It is hard not to feel, however, that the book has lost something in passing through twelve editions, which made the first edition perhaps the best as a student's text-book. This is equally true of Osler's "Practice of Medicine"; in a peculiar charm of its own the first edition surpasses all its successors. Hare's work has grown in size, but has it become really more valuable to the student or practitioner? This growth in size is always a danger to works which are "thoroughly revised" every few years. The author himself is apt to judge ill of what new material needs to be added; he often does not allow sufficient time to elapse to determine the true and permanent value of new discoveries which are daily being made. This mistake in judgment is a natural one, and with the frequent demand for a new edition, it would be almost unavoidable that both author and publisher should feel that the latest information must be set forth, though it may prove before long to be of little value. Had the author been able to give us a revised edition no bigger than the first, it would have been a still better work than the present one, which otherwise deserves all praise. It is one of the few medical text-books which can be thoroughly commended, and which every practitioner will find useful. R. N.

The New Hygiene. Three Lectures on the Prevention of Infectious Diseases. By Elie Metchnikoff. With Preface by Roy Lankester. (*Chicago: W. T. Keener & Co., 1906.*)

This little book contains three lecturers on The Hygiene of the Tissues, The Hygiene of the Alimentary Canal, and Hygienic Measures against Syphilis. They give in a very condensed space the writer's views on the three problems with which his name is most frequently associated, and to our knowledge of which he has made the greatest contributions. As Professor Lankester states in

the introduction, these lectures "should be regarded by the reader as a brief gaze into the mind and mode of work of one of the greatest living men of science." These brief lectures probably reveal more clearly than perhaps any of the writer's other works that which is perhaps at once his greatest strength and his greatest weakness, namely his tendency to construct theories, and to offer hypotheses which are so necessary for the stimulation of further research. Such men are undoubtedly of the greatest value in science. They supply the necessary imagination, which, as President Eliot has pointed out, scientific men frequently lack. Because such men frequently bring forth many hypotheses, and oftentimes persist in their defense against overwhelming evidence, we are too apt to minimize the great value of their work on scientific progress.

As might be expected, the first lecure presents a defense and a laudation of Professor Metchnikoff's favorite offspring, "the phagocytic theory of immunity." The fundamental rôle of the leucocytes in immunity has again been threatened by Wright's discovery that the serum plays an essential and primary rôle in phagocytosis. Metchnikoff, while not denying the occurrence of opsonins, presents evidence tending to minimize their importance and concludes that "we may rejoice that the foundation stone of the hygiene of the tissues, i. e., the thesis that the phagocytes are our avenue of defense against the infective germs, has at last been generally accepted." All will not agree that the evidence entirely justifies his sweeping conclusions, yet most admit that he is partly right, and are willing to forgive the exaggerations. Again, in the second lecture, very great stress is laid on the rôle of intestinal worms in the etiology of certain of the intestinal diseases. He thinks intestinal worms play an important part in the eiology of appendicitis, and even questions whether the entozoa may not serve as portals of entry for the hypothetical parasites of intestinal tumors! In this chapter one is especially struck by the tendency of the writer to lay stress on uncontrolled work and on individual observation. But while the reasoning and the conclusions are undoubtedly somewhat fanciful, and certainly at present not convincing, yet the germ of truth is undoubtedly there, and he accomplishes probably all that he intends, namely, to make the reader think. The last lecture is a discussion of the possibilities of a vaccination or specific prophylaxis against syphilis. At present nothing is definite, but it gives us a vista of the path along which the writer's mind is travelling and of his opinion as to the direction in which the goal probably lies. Any one who is interested in fundamental problems of hygiene cannot help but obtain pleasure and stimulation in reading this volume. Not much is new, but it is well said. On finishing it one has the desire to be up and doing, probably many will have the desire to show that much of it is false, but that proves that the book is of value. It is better to sometimes think wrongly than not to think at all.

Paraffin in Surgery. A Critical and Clinical Study. By WM. H. LUCKETT, M. D., Attending Surgeon, Harlem Hospital, Surgeon to the Mt. Sinai Hospital Dispensary of New York; and FRANK I. HORNE, M. D., formerly Assistant Surgeon, Mt. Sinai Hospital Dispensary. (*New York City: Surgery Publishing Company, 92 William Street.*)

The little book gives in a precise and practical way the technic of paraffin injections, and what is also of importance, discusses the causes of failures and of accidents and the means of avoiding them. The accidents which have followed the injection of paraffin have been few, but they have been serious ones, such as emboli of the lungs, and thromboses of the central artery of the retina, and they will prove a decided objection to the use of paraffin unless a way can be found to avoid them. This way the authors of this book think they have found in using paraffin with a melting point above 110° F.

A large part of the book is given up to the very interesting question of what becomes of the injected paraffin. A number of observers hold that the paraffin is soon penetrated by connective tissue in which new blood vessels are formed and that this newly organized tissue finally takes the place of the paraffin which disappears. Others, who are just as trustworthy, find even after the lapse of several years that the paraffin has not been absorbed. The authors believe that these contrary results are due to chemical differences in the paraffins used, in the varying action of the cells of the body on the paraffin, and on differences in the tissues inspected.

The second part of the book is an account of sixty-four cases of the authors, of some of which a detailed account is given. The photographic reproductions in this part of the book are very poorly done, and are not worthy of it. A full bibliography and index completes the book.

The Technic of Operations upon the Intestines and Stomach. By ALFRED H. GOULD, M. D. (*Philadelphia and London: W. B. Saunders Company, 1906.*)

In this work the author has described all the best known operations upon the intestines and stomach, with various modifications of technic which have suggested themselves to him in his experimental studies on animals and the cadaver. He has added many original illustrations to those drawn from other works on this branch of surgery, and his work will doubtless prove most serviceable to a large body of surgeons, who will find it useful to have these operations so clearly set forth in comparatively small compass. With this book at hand they will be able in a moment to find what otherwise they would have to search for in various works and then not find so lucidly explained. The author is a Boston man and has received much aid from his associates in that city, so that to a certain extent his book presents the views of the surgeons of that city, which adds to its interest. The book should be well received by the profession, for the publishers have done their part as satisfactorily as the author. R. N.

Atlas and Text-Book of Human Anatomy. Volume I. By Professor J. SOBOTTA, of Wurzburg. Edited with additions, by J. PLAYFAIR MCMURRICH, A. M., Ph. D., Professor of Anatomy at the University of Michigan, Ann Arbor. Quarto volume of 258 pages, containing 320 illustrations, mostly all in colors. (*Philadelphia and London: W. B. Saunders Company, 1906.*)

In these two volumes, now out the first devoted to "Bones, Ligaments, Joints, and Muscles"; the second to "The Viscera, including the Heart"; we have the advance publications of what promises to be a complete, I had almost said a perfect atlas for the use of students as well as practicing physicians; as the author states in his preface, "it is not for the finished anatomist, but for those who need a concise, trustworthy, graphic reference," and for these this publication seems ideal. The newer Basel nomenclature is embodied in the work with which we become readily familiar through the necessarily frequent repetitions, and the fact that the old accompanies the new.

The illustrations, and it is the Atlas which is the avowed element in the publication, are most striking, and make the perusal of the books the delightful privilege which this review has proved to be.

The author has been most generous in the number of these exquisite plates, which are good, not only from an artistic point of view, but are graphic and true.

The printers, and binders' art have combined with the author's efforts to supply a publication to which no mere review can do justice, it needs to be seen and read.

Modern Medicine. By WILLIAM OSLER, M. D. Vol. II. (*Philadelphia: Lea Brothers & Co., 1907.*)

The appearance of the second volume of the Osler system will

be welcomed by the profession and gives additional guarantee of the quality of the contributions. The volume covers a very important part of the infectious diseases. Beginning with a most interesting general introduction by Prof. Hektoen, we have a very important discussion of Typhoid Fever by McCrae, which even goes rather extensively into the surgical complications and their treatment. Among other notable sections are Councilman on Smallpox and Chickenpox, Carroll on Yellow Fever, Shiga on Bacillary Dysentery, and Acute Rheumatism by Poynton.

There is much to praise and little to criticize in the collection. The quality of the colored plates is, as in the first volume, inferior, and not up to the standard of the letter press, nor to the credit of the publishers. The photographs and black and white work are good.

Poynton, in his article naturally lays rather more stress on the "Diplococcus rheumaticus" than many competent and careful investigators are willing to concede. Ruhräh gives an excellent discussion of Measles but passes over the mooted "Fourth Disease" rather too briefly. The monograph of Musser and Norris on Lobar Pneumonia is exhaustive and contains all of importance that is in the literature. It is perhaps a little too rich in statistics.

Careful perusal of the introductory chapter and the special section on the pathology of the different specific infections will do much to explain the rational therapeutics most of the writers have suggested. It ought to give the practitioner the courage of conviction in withholding many obsolete and more new and pseudo-scientific methods of pouring in drugs to "cure" a self-limited disease, while at the same time encouraging him to observe carefully and meet rationally the emergencies as they arise.

American Practice of Surgery. A Complete System of the Science and Art of Surgery. By Representative Surgeons of the United States and Canada. Editors JOSEPH D. BRYANT, M. D., LL. D.; and ALBERT H. BUCK, M. D. Vol. III. (*New York: William Wood & Co., 1907.*)

This third volume contains Parts XI, XII, and XIII, dealing with "poisoned wounds, including the bites and stings of animals and insects," "injuries and surgical diseases of bone," and "diseases and injuries of joints." The parts are divided into chapters, each by a different author, so that there are eleven contributors to this volume, among whom are such well-known men as Major and Surgeon Charles F. Mason, U. S. A.; J. C. Oliver, C. F. Painter, Roswell Park, Duncan Coe, etc. The work is abundantly and excellently illustrated, but we fear that due to the clumsiness and weight of the volume, the articles will not receive the attention which is their due. It is a pity that this system which is so valuable as setting forth the views of many of the leading surgeons in America should not have been published in a more handy form. In such systems it is difficult to compare the relative merits of different chapters, for so much depends on the instructions given by the editors to the contributors. One writer may be allowed many pages for his article, and another far fewer, though the two subjects may seem of equal importance to many readers. The amount of space allowed to different subjects in the first three volumes seems to have been well adjusted, and there is an "up-to-dateness" in the papers which is satisfactory. Each volume is supplied with its own index. This system, with all the drawbacks common to all systems, is to be recommended to the profession. R. N.

Principles and Application of Local Treatment in Diseases of the Skin. By L. DUNCAN BULKLEY, A. M., M. D., etc. Small 8vo, 142 pages. (*New York: Rebman Company.*)

This book is the outcome of the requests on the part of his students, for Dr. Bulkley's lectures on local treatment of skin diseases, and forms a companion to his lectures "On the Relation of Diseases of the Skin to Internal Disorders."

The treatment of only seventeen diseases is given. These are characteristic, however, and serve to illustrate the principles underlying local treatment.

The work is based entirely on the author's personal experience, and naturally, some of his ideas differ from other dermatologists'. However, many excellent suggestions are offered which will doubtless prove of much value.

It is interesting to note that, though polypharmacy is decried, no less than forty drugs are mentioned in the treatment of eczema. While this, of course, is a large number, it bears eloquent testimony to the obstinacy of some cases of this disease.

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